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THE EFFECT OF RECENT ADVANCES IN BILIARY PHYSIOLOGY ON THE MORTALITY FOLLOWING OPERATION FOR COMMON DUCT OBSTRUCTION

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IN NO field of surgery has the physiologic approach to problems of pre- and postoperative care had greater influence than in the treatment of common duct obstruction. Largely on the basis of experimental studies special methods of treatment have been introduced. It is now time that we evaluate the effects of this treatment by an analysis of clinical results.

Between 1922 and 1937, 155 patients with obstructive jaundice were operated upon at the Hospital of the University of Pennsylvania under the observation of the senior author. It has not been possible to test each new addition to the treatment, but the series falls into three fairly equal chronological groups which afford comparison of three substantially different therapeutic regimes.

In addition to the effect on gross mortality, the effect on the incidence of those postoperative complications peculiar to jaundiced patients has been studied. Of these the most important is postoperative hemorrhage. "Pancreatic asthenia" and the so-called liver deaths have also been considered but their incidence is too low to permit statistical analysis in a series of 155 cases.

Group I.—The first group comprises 59 patients observed from 1922 to 1929.

These patients received small amounts of glucose by vein before operation. No consistent effort was made to raise the carbohydrate

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intake in the diet in the early years of this group, although in the final years this was done. Preoperative transfusions were not employed and after operation transfusion only rarely was resorted to unless the patient was in extremis. Biliary decompression was practically never practiced. Refeeding of bile was not practiced even when excessive quantities of bile were lost. The bilirubinemia in general was not allowed to become constant before operation. Liberal doses of calcium were routinely administered in the earlier part of this period. The usual anesthetic for operation was ether, administered by the open-drop method.

Group II.—The second group, consisting of 47 patients, was admitted between 1929 and 1933. The principal difference in treatment was the routine administration of glucose intravenously during both the preoperative and postoperative periods. High carbohydrate diets were ordered in addition, and it became the practice to make frequent van den Bergh determinations and to defer operation until a time when the bilirubinemia was constant. Blood transfusions were employed only occasionally in the preoperative period. In those patients who drained excessive amounts of bile, a portion of this bile was refed by stomach tube. Occasionally a decompression apparatus was used. The use of calcium was abandoned except in rare instances. In this group spinal anesthesia and ether were used to about the same extent.

Group III.—The third group of 49 patients covers the period from 1933 to 1937.

Glucose solutions with and without saline were given freely by vein both before and after operation. Blood transfusions were also given routinely both before and after operation. A method for gradual decompression of the biliary tract after operation was used extensively. The practice of operating only during periods of constant bilirubinemia was continued. These differences are summarized in Table I.

TABLE I

VARIATIONS IN PRE- AND POSTOPERATIVE THERAPY

GROUP	YEARS	NUMBER OF PATIENTS	HIGH CARBOHYDRATE DIET	CALCIUM	SUPPLEMENTARY INTRAVENOUS GLUCOSE		BLOOD TRANSFUSIONS		OPERATION DURING PERIOD OF CONSTANT BILIRUBINEMIA	BILIARY DECOMPRESSION	REFEEDING BILE
					PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE			
I	1922-1929	59	0	+	±	±	0	±	0	0	0
II	1929-1933	47	+	±	+	+	0	+	+	±	+
III	1933-1937	49	++	0	++	++	++	++	+	+	++

The incidence of postoperative hemorrhage, "pancreatic asthenia," and liver shock in each group and for the entire series is given in Table II.

TABLE II

INCIDENCE OF POSTOPERATIVE HEMORRHAGE, ASTHENIA, AND LIVER SHOCK

GROUP	POSTOPERATIVE HEMORRHAGE (PER CENT)	PANCREATIC ASTHENIA (PER CENT)	LIVER SHOCK (PER CENT)
I	22.0	2.0	2.0
II	19.1	2.0	4.2
III	18.4	0.0	0.0
Entire series	20.0	1.3	2.0

It appears that "pancreatic asthenia" and liver shock have been encountered with decreasing frequency. Postoperative hemorrhage, however, remains a common complication of operations upon jaundiced patients, but it has been possible to reduce the degree of the bleeding and the mortality of the complication. This is shown in Table III.

TABLE III

THE RELATION OF POSTOPERATIVE HEMORRHAGE TO MORTALITY

GROUP	NUMBER OF PATIENTS	NUMBER WITH POSTOPERATIVE BLEEDING	PATIENTS DYING PRIMARILY OF HEMORRHAGE	HEMORRHAGE MORTALITY (PER CENT)	FATAL CASES IN WHICH HEMORRHAGE OCCURRED	GROSS MORTALITY OF PATIENTS WITH POSTOPERATIVE HEMORRHAGE (PER CENT)
I	59	13	5	8.5	9	69.0
II	47	9	2	4.2	3	33.0
III	49	9	1	2.0	2	22.0

An analysis of the causes of death in the three groups is summarized in Table IV. The deaths recorded in the last column of Table IV were due to pneumonia, wound rupture, malignancy, cerebral thrombosis, peritonitis, and other conditions encountered in many types of surgical patients.

Before crediting the various therapeutic measures outlined with the improvement in mortality, it is necessary to compare the three groups in respect to age, duration of jaundice, and the type of anesthesia

TABLE IV

ANALYSIS OF DEATHS

GROUP	MORTALITY ENTIRE GROUP (PER CENT)	MORTALITY DUE TO HEMORRHAGE (PER CENT)	MORTALITY DUE TO PANCREATIC ASTHENIA (PER CENT)	MORTALITY DUE TO LIVER SHOCK (PER CENT)	MORTALITY DUE TO COMPLICATIONS PECULIAR TO JAUNDICED PATIENTS (PER CENT)	MORTALITY DUE TO OTHER CAUSES (PER CENT)
I	22.0	8.5	1.7	1.7	11.9	10.1
II	12.7	4.2	1.7	4.2	10.1	2.6
III	8.6	2.0	0.0	0.0	2.0	6.6

used. Unfortunately the data were not available in every case. Table V shows these comparisons for those cases in which the necessary information was on record.

TABLE V

GROUP	MEAN AGE	DURATION OF JAUNDICE			ANESTHESIA	
		1 TO 14 DAYS (PER CENT)	15 TO 60 DAYS (PER CENT)	OVER 60 DAYS (PER CENT)	ETHER (PER CENT)	SPINAL (PER CENT)
I	51.4	49.0	29.0	22.0	63.0	17.0
II	49.8	58.5	37.5	4.0	45.0	59.0*
III	49.9	42.5	39.4	18.1	12.0	82.0

*Some patients had ether and spinal anesthesia. The occasional use of nitrous oxide and oxygen or local anesthesia is not tabulated.

DISCUSSION

The surgery of any vital organ necessarily presents special problems related to impaired or suspended function of that organ. This is peculiarly true of surgery of the liver where one deals with an unpaired organ many of the functions of which are even now not clearly understood. There is no general agreement among physiologists on many of the functional activities of the liver and much less agreement on how others of these are accomplished. In addition, the liver has so great a functional reserve that there are no means now available of accurately discovering the extent of early stages of liver damage. None of the suggested tests of liver function gives definite significant information until the liver damage has progressed to a considerable degree. One of the most important sequelae of long standing cholecystitis and common duct obstruction is damage to the liver parenchyma. The chief mechanisms by which the damage is brought about are infection, interference with blood supply with resultant anoxemia, and the effects of pressure on the hepatic cells.

In obstructive jaundice, due to stone, there is frequently, if not always, some infection. This is evidenced by the chills and fever so regularly seen in the intermittent common duct obstruction described by Charcot.[2] The evaluation of the rôle which pathogenic organisms, commonly found in the bile, may play in liver injury needs further investigation. The flora of the biliary tract may vary, but except in suppurative cholangitis they rarely seem virulent enough to cause extensive injury unless associated with obstruction of the common bile duct or long standing cholecystitis.

The secretory power of the liver cells is sufficient to secrete bile against a pressure obstacle of as high as 270 mm. of bile. Between 280 and 330 mm. of bile pressure the secretion of bile ceases. It is probable that the distention of the intrahepatic bile ducts by pressure alone results in injury of the periductal parenchymal cells since the

liver is not capable of rapid distention. Varying degrees of obstruction to blood flow result and the anoxemia thus produced contributes still further to liver injury.[19] The observations of Levy and Blalock[11] that common duct obstruction is associated with an increased portal venous blood flow are at variance with the many observations we have made showing portal venous congestion and an increased portal venous pressure during complete ductal occlusion. The rupture of biliary capillaries may lead to areas of necrosis. The circulation may adjust itself by an increase in the portal venous pressure, but when the ductal occlusion is suddenly released massive hyperemia and extravasation may result as demonstrated by Ravdin and Frazier[16] and by Klopp and Cantarow.[10]

Over twenty years ago Opie and Alford[13] called attention to the protection which a high carbohydrate diet afforded the liver against the necrotizing effects of chloroform. Since that time it has been supposed that the presence of an adequate liver glycogen protected the liver against the injury imposed by volatile anesthetics. In work soon to be reported from this department it will be demonstrated that a greatly increased glycogen level does not protect the liver against injury if there is simultaneously present a high level of the liver fat. Although in general the Rosenfeld[20] hypothesis of a reciprocal relationship between liver glycogen and liver fat may be maintained, we have encountered so many exceptions to this generalization that it is not safe to conclude that a high liver glycogen concentration necessarily indicates a low liver fat concentration. Furthermore, should chronic liver injury result in an increased content of liver fat, it may be more difficult to displace the fat by the simple administration of carbohydrates. Goldschmidt, Vars, and Ravdin[6] have stated that the amount of fat present in the liver is the most important factor in conditioning necrosis following the administration of fat soluble anesthetics and that the protective rôle of the carbohydrate depends upon displacement of the liver fat during the deposition of liver glycogen.

It is less easy to explain why glucose decreases the clotting time in obstructive jaundice[17] and why, even though it may not affect bleeding or clotting time, it seems to reduce hemorrhage mortality. Clinicians are agreed, however, that the patient with a damaged liver fares better on a high carbohydrate intake. It is generally agreed that the main object of carbohydrate therapy is to produce a high glycogen level in the liver, but it is not so generally understood by clinicians that the success of this therapy depends in large part upon the simultaneous displacement of liver fat. It is often difficult to do this in the presence of common duct obstruction as evidenced by sections of the liver from some of the patients in Group III of this series (Fig. 1).

In 1929 Ravdin[15] recommended that intravenous infusions of glucose be used to supplement a high carbohydrate diet in the preopera-

tive period. Experiments, soon to be reported, have shown that in the dog it is possible with large intravenous glucose infusions and strenuous oral administration of carbohydrates to produce a high liver glycogen in dogs whose common ducts have been obstructed. Admittedly this form of obstruction is often not comparable to the clinical types where even more intensive therapy is necessary.

Of all the problems peculiar to the surgery of jaundice, none has received more attention than the tendency to hemorrhage. This tendency may be so marked that spontaneous bleeding may occur from the mucous membranes. Usually, however, it occurs from the operative site, sometimes from the wound, sometimes from the bile passages, and sometimes from both.

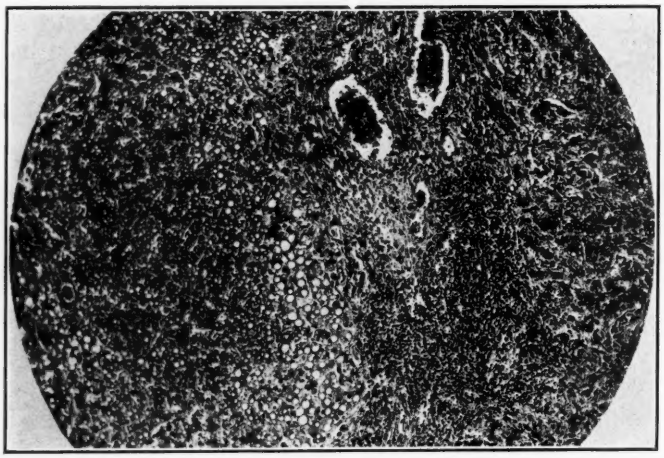

Fig. 1.—Photomicrograph of autopsy specimen of liver from a patient with long-standing common duct obstruction after thorough pre- and postoperative treatment with carbohydrates.

Many authors have regarded this bleeding tendency as due to a deficiency of some of the normal constituents required for the clotting process. Gunther and Greenberg[7] have shown that neither the ionized nor nonionized calcium is deficient in the blood of patients with common duct obstruction unless there is an associated serum protein deficiency, when only the nonionized calcium level is disturbed.

It is not improbable that in children, as in young dogs, a low calcium level frequently accompanies jaundice and it is true that the serum calcium is frequently lowered in the presence of hypoproteinemia; but the serum protein is markedly low in only the exceptional adult patient with obstructive jaundice. We do not feel that the experimental data or our clinical experience justifies the preoperative use of calcium and we have abandoned its use since 1932 except in children and in the presence of hypoproteinemia.

The recent investigations of Nygaard[12] and Quick and others[14] indicate a deficiency of prothrombin in the blood of the jaundiced patient, but Eagle[4] has not been able to demonstrate a prothrombin deficiency in the blood of animals with obstructive jaundice. The recent suggestion that vitamin K may be deficient in these patients is of considerable interest.

Not only has the cause of the hemorrhagic tendency remained obscure but innumerable attempts to determine preoperatively which patients will and which will not bleed have been in the main unsuccessful.

Several general considerations are believed to influence the hemorrhagic tendency. Thus, it is believed that the duration of the jaundice is a factor in producing the hemorrhagic tendency. The data compiled from this series of cases lend some support to this belief (Fig. 2).

As in all other hemorrhagic diatheses, recourse is ultimately had to transfusion. In the third period of our clinical study, transfusion has

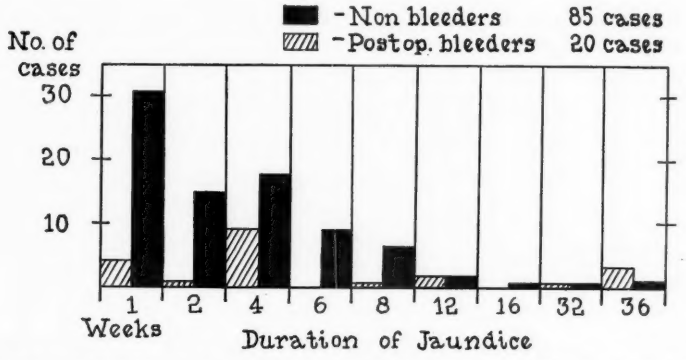

Fig. 2.—The relation of the duration of jaundice to the incidence of postoperative hemorrhage.

been used prophylactically. The fact that the incidence of hemorrhage has not declined would seem to throw serious doubt on the advantage of preoperative transfusion without other indications, such as anemia. However, we believe that, although the hemorrhage incidence has remained the same, the degree of hemorrhage has been markedly reduced, and that we have been less alarmed by the extent of the bleeding. In fact, we have recorded some instances of postoperative bleeding that might have been disregarded by some observers.

The occasional occurrence of hypoproteinemia in patients with biliary tract disease and the frequent association of hypoproteinemia with delayed wound healing[21] we believe would especially indicate transfusion before operation. No doubt serum transfusion would serve as well for this purpose as whole blood.

Progressing from the preoperative measures based on scientific experiments toward those based solely on clinical experience, one comes finally to the selection of the time for operation with respect to the

level of the van den Bergh test. It has long been customary to postpone operation in the face of decreasing jaundice as long as the serum bilirubin continues to fall. It has been found wiser, however, similarly to postpone operation, if the jaundice is increasing, until a constant bilirubin level has been reached (Walters[22]).

The anesthetic agent used for operation undoubtedly has a very important bearing on the patient's recovery. Obviously the known anesthetics causing liver injury, chloroform, avertin, and divinyl ether are contraindicated. As prolonged diethyl ether anesthesia, especially when associated with anoxemia, is capable of producing similar liver injury,[5] we believe that it is to be avoided when possible.

The studies of Rich[19] and Goldschmidt, Ravdin, and Lucke[5] indicate that the liver cells are exceedingly sensitive to a reduced oxygen tension. If this be true, the use of any gas mixtures, which do not provide ample oxygen in the blood, is likely to be harmful. We have no evidence that cyclopropane is harmful though, like local anesthesia, it is unlikely to permit sufficient relaxation for adequate exposure.

The anesthetic of choice, we believe, is spinal anesthesia. The chief drawback, that of a drop in blood pressure with reduction in blood flow through the liver and resultant liver anoxemia, may be overcome in most cases by the use of ephedrine preoperatively.

During the postoperative period, the problem of liver insufficiency may persist in even greater degree because of trauma and anesthesia and treatment during this period must be designed to meet this. The glucose intake must be kept up and as the patient seldom takes much by mouth during the initial phase of the postoperative period a continuous venoclysis of a glucose solution should be given. A high carbohydrate diet should be given as soon as possible.

The problem of keeping up the oxygen supply of the liver parenchyma presents several important aspects. It is of prime importance in this regard to maintain the respiratory exchange and to prevent atelectasis or other pulmonary complications. To this end it is the rule to insist on hourly change in position and hourly deep breathing exercises reenforced, if cooperation is not forthcoming, by inhalations of oxygen (90 per cent) and carbon dioxid (10 per cent). Any tendency for mucus to collect in the bronchial tree is combatted with expectorants, steam inhalations, and regular encouragement of the patient to cough. To reduce incisional pain during coughing, a tight binder is applied and often an attendant supports the patient's abdomen with his hands during the attempts to cough up the mucus. Atropine is not employed as we believe it makes the bronchial secretions thicker and more likely to occlude the bronchi.

A transverse or subcostal incision is used routinely which seems to permit abdominal respiration sooner than the right rectus incisions. On the basis of the statistics collected by Ravdin and Kern,[18] every reasonable endeavor is made to complete the operation in as short a

time as possible. In occasional instances patients have been given oxygen therapy after operation with the hope that higher oxygen tension would lead to better oxygenation of the liver cells.

Anemia should be corrected preoperatively and if much blood loss is sustained at operation, it should be promptly repaid by transfusion. It is of particular importance to prevent any depletion of blood volume as the resultant circulatory adjustment may seriously lower the arterial oxygen tension and blood flow to the liver may be seriously reduced.

The importance of biliary decompression has already been referred to and is discussed fully by Ravdin and Frazier.[16] While admitting the theoretical advantages of clamping the common duct before it is opened as recommended by Culligan,[3] the practical disadvantages of this maneuver have yet to be overcome. After the tube is sutured into the common duct, decompression should be carried out by a continuous method rather than by the intermittent method of Culligan.

The incidence of "pancreatic asthenia" became extremely low with the introduction of the practice of refeeding bile to patients with prolonged excessive bile drainage. By increasing the pressure in the drainage tract with a decompression apparatus, the excess bile can usually be forced into the duodenum, thus obviating the cumbersome method of refeeding bile through a stomach tube.

"Liver shock," like "pancreatic asthenia," has become a rare complication. As a condition similar to "liver shock" regularly appears in dogs when the hepatic artery is ligated, it seems possible that this condition is related to liver anoxemia. It would seem possible that an occasional instance of human liver shock might be due to unintentional ligation of an hepatic artery or to thrombosis of this vessel during convalescence. This condition is included by Heyd[8] and by Boyce and McFetridge[1] in their discussions of so-called liver death. It is nearly always encountered in the group of patients who die within forty-eight hours with high fever.

These authors describe a second symptom-complex, the hepatorenal syndrome, which they consider a later phase of the same process. This is characterized by increasing oliguria leading to anuria and terminal uremia, ten to fourteen days after operation. Only one patient in this series died in uremia. No autopsy was obtained, and it has been impossible to determine whether this case belongs in this group.

The largest single factor in the operative mortality of jaundiced patients was hemorrhage. This occurred in about 20 per cent of the patients in each of the three groups but resulted fatally in a decreasing percentage in the later groups. The treatment of hemorrhage has been transfusion. In one case twenty-two transfusions were given before a favorable outcome was achieved. Locally attempts have been made to check the hemorrhage with stryphnon gauze packs, but packing usually accomplishes little. When hemorrhage from the ducts persists

for several days, it may be wise to remove all the drainage tubes, including the tube from the common duct.

After the release of common duct obstruction, several weeks may pass before the liver bile shows evidence that hepatic function has returned to normal. A high carbohydrate intake should be maintained not merely until jaundice has disappeared but until bile salts have reappeared in good concentration and the cholesterol concentration returns to normal in the bile. Except in the face of persistent hemorrhage over a considerable period, the common duct tube should not be removed until these changes can be demonstrated. It is also routine to inject the tube with lipiodol for x-ray visualization of the common duct before its removal.

The lag period between the release of obstruction and the recovery of liver function cannot be too strongly emphasized. Judd, Snell, and Hoerner[9] have reported bleeding in patients in whom jaundice was no longer present but in whom liver injury remained. A similar case was observed in the Hospital of the University of Pennsylvania in 1936.

CONCLUSIONS

1. A group of 155 patients operated on for obstructive jaundice has been analyzed for the effect of a changing pre- and postoperative regime on morbidity and mortality.

2. The operative mortality has been greatly reduced.

3. The incidence of postoperative hemorrhage has not been influenced by changes in our preoperative preparation; but the degree and extent of the hemorrhage have been influenced and the mortality from postoperative hemorrhage has been markedly reduced.

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APPLIED PHYSIOLOGY OF LIVER

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TO APPRECIATE the advances made within the last three decades in our knowledge of the functions of the liver, one need only turn to the first essentially modern textbook of physiology (Schafer, 1898). The general principles of carbohydrate and protein metabolism had been laid down, but little was known of the metabolism of fat in this organ, of the secretion of bile aside from the general chemical constitution of this fluid, or of the many other functions of the liver. Little of the information available was capable of clinical application. Since the turn of the century, details have been supplied in those fields where only broad generalizations had been available, and many facts directly applicable to medical practice have been discovered. As is the case in all branches of science, discoveries that possess great practical significance may be in themselves but minor details of the general picture, and are often entirely dependent upon an immense amount of previous experiment and observation which has but little immediate applicability.

Notwithstanding the advances that have been made, the functions of the liver remain one of the least developed frontiers of medicine. When the liver is removed surgically, death ensues within about twelve hours unless glucose be given to maintain the blood sugar level. But even though the normal blood glucose range be maintained, death cannot be postponed more than twenty-four to thirty-six hours at the most. The cause of the fatal termination which then occurs is unknown. And it is significant that this is true of no other organ in the body; in every other instance either the cause of death is known or replacement therapy is effective. Contributions dealing with new aspects of hepatic activity are frequent; for example, only within the last few years has it become apparent that the liver is primarily concerned with the metabolism of oxalic and citric acids. Although such accretions to our information may not be immediately applicable, they serve to fill in the picture which, as it grows more and more complete, will increasingly permit the treatment of hepatic disease to be placed on a sound and logical basis.

As new facts are discovered, there is a tendency to attempt an immediate application for the purpose of testing liver function. The

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obstacles facing a "liver function test" have often been emphasized. The large factor of safety, some 80 per cent of the organ being removable without apparent change; the diversity of functions, giving no assurance that impairment of one function means deficient activity of the organ as a whole; the difficulties of experimental investigation and especially of clinical study; all these complicate a study of the functions of the liver and even more seriously disturb an evaluation of the state of those functions by arbitrary tests. A discussion of the liver is most conveniently divided according to the various types of metabolic activity with which this organ is concerned. Since it is questionable whether any of our present tests of liver function are satisfactory, these are best included in the discussions of those functions which they purport to evaluate.

THE SECRETION OF BILE

Since cholecystitis and cholelithiasis are more common than any other biliary tract disease and are apparently far more common than all affections of the liver itself, the gall bladder has attracted more clinical interest than any other part of the liver and biliary tract system. Ray[1] has recently analyzed a large number of human gallstones and finds no essential difference in chemical constitution between those that have been referred to as calcium-cholesterol-pigment stones and those called cholesterol-pigment stones. Stones from the same gall bladder were always very similar and even stones of different appearance and of presumably different types did not vary in any consistent or striking manner. Riegel and others[2] have since found calcium to vary from traces to 28 per cent, while the cholesterol values given are usually above 70 per cent. Even such variations do not necessarily bespeak multiple causes for calculus formation, while Ray's conclusions are compatible with the concept that a single factor may be the primary cause. Walsh and Ivy[3] have discussed the various theories that have been proposed and have come to the conclusion, which must be that of any impartial observer, that at present no definite decision can be reached concerning the relative importance of pH, stagnation, decreased concentration of bile salts, and other possible factors in human cholelithiasis.

A consistent and striking observation is the decreased concentration of bile salts found when stones are present in the gall bladder or when the gall bladder is damaged.[4-7] Since the bile salts are essential for the solution of all the lipids in bile, including cholesterol, the demonstration of a decrease in bile salt concentration is strongly suggestive of a direct relationship of this change to stone formation. It should be noted also that both bile salt and cholesterol concentration have been found by Riegel, Ravdin, and Rose[8] to be decreased in the biliary

drainage of patients with liver damage; the decrease in bile salt concentration was proportionately greater than that of cholesterol. Bollman and Mann[9] have produced evidence that the liver is the sole site of bile salt formation, that it plays the major rôle in the destruction of bile salts, and that liver poisons, such as chloroform, carbon tetrachloride, or tetrachlorethylene, can produce such a marked decrease in bile salt formation that only traces are present in the bile. If one considers the tempting hypothesis that the mechanism of stone formation is a precipitation of fatty acids and cholesterol secondary to a decrease in bile salt concentration, then it appears that this decrease may occur either as a result of impairment of liver function or because of increased absorption of bile salts through the wall of a damaged gall bladder.[2, 7]

An important consideration arising from the demonstration that the production of bile salts may be so greatly decreased by liver damage is the questionable value of returning such bile to the gastrointestinal tract as is the usual practice in cases of biliary fistula. The value of bile for the digestive tract, according to all information, lies in its bile salt content. It would seem far more beneficial to administer bile salts by mouth in the maximum dosage tolerated than to return drainage bile in which the bile salt concentration may be negligible.

It should be noted that Golber[10] has observed an increase in cholesterol and a decrease in bile salt in the bile in thyrotoxicosis, and discusses the bearing on gallstone formation. Riegel and others[11] have removed specimens of gall bladder bile from living pregnant women at term and found an increased cholesterol and decreased bile salt content; this suggested to them both a change in the character of the liver bile and a decrease in the absorptive ability of the gall bladder. Hawkins and Whipple,[12] in a recent review of their investigation on dogs with biliary fistulae, note that cholelithiasis may occur in such animals if they are not given bile by mouth. This might be attributed to a decrease in bile salt concentration as a result of long continued drainage.

The presence of bile in the intestine aids in the hydrolysis of fats by lipase and is essential for normal absorption of the fatty acids. Greaves and Schmidt,[13] confirmed by Taylor, Weld, and Sykes,[14] have shown that bile (bile salts) is essential for the absorption of vitamin D. Later Greaves and Schmidt[15] showed that while vitamin A can be absorbed from the intestine in the absence of bile, carotene (the precursor of vitamin A) cannot. Exclusion of bile from the intestine therefore may be expected to result in decreased fat absorption and possible vitamin A and D deficiencies. Hawkins and Whipple[12] have shown that in biliary fistula dogs one may find not only the cholelithiasis mentioned above but also purpura, possibly due to lack of prothrombin,

osteoporosis which may be secondary to a vitamin D deficiency, duodenal ulcers, and intestinal intoxication. Liver feeding much improved the general condition of their animals. While such disturbances as these may be anticipated in patients with bile fistulae, the more common condition of jaundice with partial or complete exclusion of bile from the intestine is an even more complex syndrome. Ivy[16] has reviewed the disturbances incident to jaundice. Quick and others[17] have since found the prothrombin content of the blood decreased in this condition, which may serve to explain the increased tendency to hemorrhage, the reason for which has not previously been clear.

The most serious aspect of jaundice, and that responsible for much of its symptomatology, is the associated disturbance of liver function which obviously is primary in toxic or infectious jaundice and is inevitable as a secondary result of an obstructive jaundice which persists for any length of time. It would seem that the surgeon assumes a considerable risk in operating upon a patient with known hepatic pathology or with biliary tract disease of such long standing that liver function may be presumed to be impaired.

Quick[18] has found his hippuric acid excretion test for liver function negative in obstructive jaundice of short duration, as it usually is in cholecystitis and cholelithiasis, but as complete obstruction persists there are pathologic changes in the liver, increasingly severe functional impairment of that organ, and eventual death. Cantarow and Stewart[19] state that the intravenous administration of sodium dehydrocholate to cats with ligated common bile ducts decreased the regressive lesions in the liver, produced persistence of the stainable lipids, and aided in maintaining the serum bilirubin.

CARBOHYDRATE METABOLISM

Clinically, the most important aspects of hepatic carbohydrate metabolism are (1) the importance of the liver for the regulation of the blood sugar level, so that in any instance of hypoglycemia it is necessary to consider whether it may not be of hepatic origin; and (2) the importance of an adequate glycogen store for the maintenance of normal liver function and the value of promoting glycogen deposition in the management of hepatic disease.

The hypoglycemias that accompany adrenal and pituitary insufficiency in all probability are due to failure of the liver to liberate glucose into the blood at the normal rate. Crandall and Cherry[20] have shown that after hypophysectomy the amount of glucose added to the blood by the liver is less than normal and that in hypophysectomized or adrenalectomized animals the liver does not respond to insulin hypoglycemia in a normal manner by the liberation of increased amounts of glucose. In the normal animal hypoglycemia causes an

increase in the production of glucose by the liver; this is not true in adrenal or pituitary insufficiency. Thus, it is clear that the liver is the primary factor in the regulation of the normal blood sugar level; that is, it is the major factor in the homeostasis of the blood glucose.

When glucose is absorbed from the intestine, the liver carries on its homeostatic activity by stopping the formation of glucose and by removing a considerable amount of this sugar from the portal blood.[21] In this way an excessive hyperglycemia after glucose ingestion is prevented. In spite of these known activities function tests based on glucose administration have been of little value; too many other factors enter into blood sugar regulation.

The importance of gluconeogenesis (the conversion of nonsugars, such as lactic acid, amino acids, glycerol, etc., into glycogen or glucose) for the maintenance of the glucose supply of the body is illustrated by the decrease in glycosuria which occurs when diabetics develop cirrhosis of the liver.[22] In confirmation of such clinical observation it has been shown that experimental liver injury reduces glycosuria in the depancreatized dog,[23] while hepatectomy causes an abrupt fall in blood sugar in the diabetic animal.[24] It is probably a failure of gluconeogenesis which is responsible for the decreased glycosuria after hypophysectomy or adrenalectomy in experimental diabetes.[25] Patients with hepatic disease require increased amounts of sugars in the diet, best given in the form of glucose, not only to promote the storage of glycogen but also to meet the normal glucose requirement of the body since the liver becomes incapable of a normal production of this sugar from noncarbohydrate sources. In view of the diminished glycogen storage capacity present in liver disease, the administration of glucose should be as nearly continuous as possible in severe cases. But there would seem to be no need of intravenous injection unless the oral route is impractical.

In recent years the importance of producing maximal glycogen deposition in the presence of hepatic disease has been emphasized. A high glycogen content seems to improve the ability of the liver to carry out its various functions, and high carbohydrate diets have become accepted therapy. Both Ravdin[26] and Stone[27] have shown that liver regeneration is most rapid on those diets which permit the greatest deposition of glycogen. Stone has also observed that on starvation the liver glycogen fell most abruptly and to the lowest levels in those animals that had been receiving high carbohydrate diets. This illustrates the importance of constantly maintaining a high carbohydrate intake in the presence of severe hepatic pathology. Jones[28] has emphasized the marked improvement in the results obtained in the treatment of various types of hepatic disease since the introduction of intensive glucose therapy.

Many of the substances which are used by the liver for gluconeogenesis, such as amino acids and lactic acid, as well as other sugars (levulose and galactose) which are converted into glucose by the liver, have been used in testing liver function. In general it may be said that hepatic activity must be much impaired before positive results are obtained. While such tests fail to detect early and slight hepatic involvement, the use of galactose or levulose may aid in differentiating infectious from obstructive jaundice, since they are not positive in the latter unless pathologic changes have occurred secondary to long continued obstruction.

LIPID METABOLISM

It is not yet known whether the liver is essential in the metabolism of fats, but there is no question that it plays an important rôle. A striking fact that seems to have been insufficiently emphasized is the change in fat deposition in human liver disease and experimental liver injury. A loss of fat from the subcutaneous tissues, giving a loss of skin turgor and a wasted appearance that may be mistaken for dehydration, is often seen in those cases of cirrhosis where hepatic function seems to be gravely disturbed. A similar loss of subcutaneous and depot fat in Eck fistula dogs is mentioned by Crandall and Anderson,[29] who showed that the appearance of these animals is not due to dehydration. Crandall and Ivy[30] have briefly discussed the low blood lipoid level of Eck fistula animals and the decreased response to oral fat administration. The loss of depot fat, however, remains unexplained.

It is well known that extensive deposition of liver fat may occur after the administration of hepatotoxins such as chloroform, or in the absence of the external secretion of the pancreas, and it has been shown also by the extensive studies of Best and his collaborators to develop when the choline and betaine content of the diet is minimal. Choline or betaine prevents the abnormal accumulation of liver fat that otherwise occurs after pancreatectomy in experimental animals; it also can prevent the deposition of fat on high fat or high cholesterol diets.[31, 32] Since extensive fat accumulation in the liver depresses hepatic function, choline or betaine may be found clinically useful, especially in cases where liver lipid deposits are believed to have resulted from pancreatic fibrosis with lack of external pancreatic secretion. More recently Dragstedt, Prohaska, and Harms[33] have found a substance, apparently not a choline derivative, in defatted alcoholic extracts of pancreas which prevents the development of fatty livers in depancreatized dogs; they suggest that this substance may be a hormone and have termed it "lipocaic."

It seems well established that the liver is the site of ketone body formation. It is not surprizing, therefore, that hypophysectomy should

diminish or abolish ketone body excretion, as it does the glycosuria, in experimental diabetes.[34] On this basis an attempt has been made to treat human diabetes by subjecting the pituitary gland to deep x-ray therapy. Such a procedure seems unjustified, for while removal of the hypophysis may suppress the ketogenesis and glycosuria of experimental diabetes, it does so only by superimposing a second metabolic abnormality upon that already existing.

RELATION TO BLOOD FORMATION

The liver stores substances which are essential for the normal formation of the red cell stroma (antipernicious anemia factor), hemoglobin (antisecondary anemia factor), and also stores iron. It also plays a large part in the formation of the blood proteins, especially fibrinogen and albumin, and is concerned in the production of those substances other than fibrinogen that are essential for the clotting mechanism. It is important for the regulation of the circulating blood volume and the prevention of excessive dilution after fluid administration.[35]

It has been shown by Ivy[36] that while the liver of the untreated pernicious anemia patient contains little or no anti-PA factor, storage may occur readily when liver extract is given. It is possible, however, that in liver disease the retention of this substance is diminished, for Rosenberg[37] has described a macrocytic anemia occurring in such cases that may be difficult to differentiate from pernicious anemia, and Goldhamer, Isaacs, and Sturgis[38] have found decreased storage of the anti-PA factor in cirrhosis. The anemia is seldom as severe as that which may occur in untreated pernicious anemia but is similar in type. Whipple and Robscheit-Robbins[39] find that the effectiveness of human liver in promoting hemoglobin formation (and hence presumably the storage of the antisecondary anemia factor) is much decreased by the presence of parenchymal injury. Thus it seems that while liver disease may decrease the storage of both factors, the more important effect is on the stroma-producing (anti-PA) substance, since the anemia that develops is of the primary type. The factor of safety that is present in the relation of the liver to blood formation, as in other liver functions, is illustrated by the observation of Daft, Whipple, and Robscheit-Robbins[40] that only in very severe or fatal experimental liver injury is there a decrease in hemoglobin formation, if iron is given intravenously.

The inability of the diseased liver to form blood proteins normally, as shown by Kaunitz,[41] Ipanov and Chervyakovski,[42] and Kasugai,[43] especially the decreased formation of albumin which results in a disturbance of the albumin-globulin ratio, seems to be the basis of the Takata-Ara reaction which was first used empirically. Unfortunately,

the Takata-Ara test is not as specific as might be desired, being positive in certain infectious diseases.

GENERAL CONSIDERATIONS

It is striking that so many types of liver injury (Eck fistula, ligation of common bile duct, bile fistula, hepatotoxins) are followed in many instances by ulcerations of the duodenum which are chronic and have many of the characteristics of human "peptic" ulcer. Correspondingly, most of the methods employed to produce experimental peptic ulcer seem to depend upon interference with hepatic function. Crandall and Ivy[30] have reviewed this apparent relationship between ulcer and liver damage and conclude that, while the question is still obscure, the evidence is so suggestive that further intensive study is indicated. In the same article these authors have discussed the relationship of liver disease and experimental injury to pathologic changes in the central nervous system.

Other functions of the liver, i.e., protein metabolism, vitamin storage, relation to mineral balance, pigment metabolism, etc., have undergone many advances in recent years but few clear cut clinical applications have been developed. It is not known how hepatic disease may affect the storage of vitamins A and D, although Knöpfelmacher and Reiter[44] were unable to show that liver injury decreased the conversion of carotene to vitamin A. Addis, Poo, and Lew[45] have shown that storage of protein occurs in the liver to a proportionately greater extent than in any other organ.

In conclusion we should again emphasize the importance to the surgeon in evaluating the degree of hepatic insufficiency that may be present before he undertakes any surgery upon the biliary tract. In view of the unfortunate accidents that so often complicate such operative procedures, it would seem that a preliminary evaluation of liver function is indicated. The bilirubin clearance[46] is perhaps the most sensitive test, although it is valueless in the presence of jaundice. If the hippuric acid test[18] is definitely positive or if the venous stasis bleeding time[47] is much prolonged, or if other tests show impairment of liver function, the increased surgical risk must be taken into consideration.

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NONCALCULOUS CHOLECYSTITIS

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THERE is perhaps no disease which is more variable in the severity of symptoms manifested than is cholecystitis. Although gallstones are probably the most common type of lesion capable of producing symptoms, there are nevertheless numerous other types, much less clearly understood, which can produce serious trouble. It is likewise noteworthy that there is scarcely any other disease in which the relationship between the pathologic findings and amount of symptoms is so variable and inconstant. These features are largely responsible for the difficulty encountered in arriving at a decision relative to advisability of operation, etc., particularly in the noncalculous type of cholecystitis.

During recent years reasonably satisfactory proof has been offered of the existence of a new disease entity which has been called biliary dyskinesia, the principal feature of which is a spasm of the sphincter of Oddi. Acceptance of this new type of biliary disorder scarcely allows us to apply the term noncalculous cholecystitis to the entire group of patients to be discussed in this study because of the location of the offending lesion outside the gall bladder. However, there does not appear to be a better term available, particularly since most workers on this subject consider the term noncalculous cholecystitis an inclusive one.

For many years various authors, from time to time, have called attention to the fact that better results were to be expected (Judd,[1] Lahey,[2] and others) following cholecystectomy if symptoms were severe, i.e., of the nature of biliary colic. During the past few years it has become apparent, from various reports published, that the results of cholecystectomy (likewise cholecystostomy) are so unsatisfactory in patients with noncalculous cholecystitis that serious effort should be made to discriminate more closely as to when cholecystectomy should be advised. In a study of cholecystectomies for stoneless gall bladder, Graham and Mackey[3] noted that only 60 per cent of the patients considered themselves relieved of symptoms by the operation. In a similar study Lehman and his associates[4] noted that after cholecystectomy satisfactory results were obtained in 70 per cent of patients with stones; whereas in the patients without stones satisfactory results were obtained in only 64 per cent. The percentage of favorable results in the noncalculous group reported from each of these two

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clinics is discouragingly low, but remarkably similar, and probably represents a fair estimate of the results obtained throughout the country in the noncalculous type of cholecystic disease. The seriousness of the poor surgical results in noncalculous cholecystitis becomes more apparent when we stop to realize that one-third to one-half of the cholecystectomies performed throughout the country are performed upon patients without gallstones. The realization that such a large percentage of patients submitted to cholecystectomy have a poor prognosis staring them in the face is sufficient to stimulate an enormous amount of thought and effort in an attempt to eliminate the poor results. It is obviously incorrect to discredit the operation of cholecystectomy on all patients without stones in their gall bladders, since it is well known that practically all the variations of pathologic processes, including even gangrene with perforation of the gall bladder, may be encountered in cholecystitis without stone. Analysis of the group of unfavorable results following cholecystectomy in noncalculous cholecystitis by numerous authors reveals the fact that the poorest results are obtained in the group with mild pathologic findings, in which there is no history of significant gall bladder pain or colic and perhaps a doubtful cholecystographic diagnosis, such as might be made on faintness of shadow. Graham and Mackey noted that in their group of stoneless cases 76 per cent of their patients giving a history of gall bladder colic were relieved; whereas only 58 per cent of those without colic sustained satisfactory results following cholecystectomy.

It is agreed by practically all observers, particularly those making a study of noncalculous cholecystitis during the past few years, that a large percentage of failures following cholecystectomies in patients without significant biliary colic is due to an *erroneous diagnosis*. This feature has been stressed by Wier and Snell,[5] Stanton,[6] and others, all of whom have repeatedly warned against the frequency of these errors in diagnosis. The fact remains, however, that the manifestations produced by the disease which have confused the issue, are often more typical of cholecystitis than the manifestations of many cases of proved cholecystitis. The situation is made much more complicated by the fact that cholecystitis, being such a frequent disease, is very apt to be encountered along with another disease which may be much more serious than the cholecystic disease itself. A list of the diseases with which cholecystitis may be confused is so limitless that their differential diagnosis cannot be considered here. The more common diseases in this group include such lesions as carcinoma of the colon, peptic ulcer, carcinoma of the stomach, pancreatitis, carcinoma of the pancreas, constipation, colitis, cirrhosis of the liver, intestinal allergy, tuberculosis of the spine, renal disease, etc.

Stanton has made a particular study of the patients in his series upon whom the diagnosis was incorrectly made. In his series of cholecystectomies he noted that of 90 patients followed for a period of years only 67 (or 74.5 per cent) made a complete recovery. Moreover, in this group of 67 cases obtaining relief from cholecystectomy, the diagnosis was discovered to be erroneous in 19. I am inclined likewise to believe that an erroneous diagnosis explains the majority of poor results and I doubt that actual figures in other clinics would differ significantly from those of Stanton.

It cannot be disputed, however, that there is a large group of patients suffering from noncalculous cholecystic disease who are relieved by cholecystectomy. This group must not be deprived of the relief which may be offered them. As already stated, we must learn to differentiate the favorable from the unfavorable group and we must learn not to operate on the group which previously has yielded such poor results.

TYPES OF LESIONS ENCOUNTERED IN NONCALCULOUS CHOLECYSTITIS

The types of noncalculous lesions of the gall bladder capable of producing symptoms can be divided into six groups; one of these groups (cholesterosis), as will be pointed out, may be insignificant in the production of actual symptoms. Because of the wide variation in manifestations and uncertainty as to whether the pathogenesis of acute and chronic inflammation is the same, these two lesions will be considered separately.

1. *Acute Inflammation.*—Practically every phase of acute cholecystitis associated with calculi may be found in acute noncalculous cholecystitis. The actual mechanics of the production of the acute inflammation are no doubt different in calculous and noncalculous cholecystitis, but the pathologic and clinical results may be quite identical. Nevertheless, it is a well-known fact that the majority of patients suffering from acute cholecystitis have gallstones. This implies, and correctly so, that stones are a very important factor in the pathogenesis of acute cholecystitis.

In a series of 38 patients with gangrenous cholecystitis reported by Mentzer,[7] 10 cases were noncalculous in origin. In a study of 160 cases of acute cholecystitis Whipple[8] noted that 30 (18 per cent) had no stones. However, an analysis of numerous reports in the literature scarcely bears out such a high figure; it is doubtful if more than 10 per cent of patients with acute cholecystitis have no stones in their gall bladder.

Bacteriologic studies made from the wall and lumen of the acutely inflamed gall bladder persistently have revealed a surprisingly low percentage of positive cultures (somewhat greater than 50 per cent). This fact has led certain observers (Denton and Feinbatt) to suspect that in a huge percentage of instances acute cholecystitis was not pri-

marily of bacterial origin. Andrews[9] has noted that acute cholecystitis can be produced experimentally by injecting bile into the gall bladder "in concentrations only one or two per cent more than the six or eight that are found in normal human bile." The fact that cholecystectomy can be performed in the presence of acute cholecystitis with a relatively low mortality and without development of infection supports the idea that infection is by no means the only important mechanism in the pathogenesis of acute cholecystitis.

The manifestations produced by acute noncalculous cholecystitis are so slightly different from those produced by acute calculous cholecystitis that they need not be described in detail here.

However, in a recent report Wolfson and Rothenberg[10] remark that patients with noncalculous acute cholecystitis "appear sicker, more frequently have chills, and maintain a higher temperature range than those with acute cholecystitis caused by cystic duct stone." They noted also that dyspepsia, belching, aversion for fatty food, and a history of previous attacks were not as common in patients with acute noncalculous cholecystitis as in those with acute calculous cholecystitis. The above-mentioned differences will not be constant enough, however, to be of great value in the determination of presence or absence of stones in the gall bladder when an acute inflammation is present. Perforation of the abdominal wall secondary to gall bladder disease is perhaps an exception to this statement since stones or carcinoma are usually present when this happens; in the latter instance, i.e., carcinoma, stones likewise are present.

2. *Chronic Inflammation.*—Obviously on many occasions chronic cholecystitis is the direct result of a partial subsidence of an acute cholecystitis, regardless of the primary factor. On some occasions the adhesions which were a direct result of the acute inflammation are the only residue of the inflammation. These may or may not be a residue of chronic inflammation throughout the adhesions and scarred areas and symptoms may or may not be produced by them. In reality then, on many occasions healing has taken place quite completely and the adhesions represent merely a scar, just as a scar forms on the skin after a laceration or infection heals. The term pericholecystitis has been assigned very appropriately to this lesion. Although experience has taught us that many gall bladders with pericholecystic adhesions will function properly as far as concentration (as determined by cholecystography) is concerned, yet a large percentage of individuals in whom pericholecystitis has been found will complain of dyspepsia or colicky pain or both. Pericholecystitis produced by lesions outside the gall bladder (e.g., duodenal ulcer) is perhaps slightly less apt to produce symptoms because there is no involvement of the cystic duct or mucosa and submucosa of the gall bladder.

In the majority of instances chronic noncalculous cholecystitis, as characterized primarily by thickening of the gall bladder wall and lymphocytic infiltration, does not arise as a sequel of acute inflammation but develops insidiously. From the standpoint of deleterious effects on the patient, it makes no difference whether the inflammation is of chemical or bacterial origin. The mechanism of the development of the bacterial type of inflammation has been presented by Graham and Peterman[11] and others. In either the chemical or bacterial chronic cholecystitis the wall may be so badly damaged as to destroy practically entirely the function of the gall bladder, particularly when we consider that the region about the cystic duct likewise becomes involved not only by edema but by actual inflammatory tissue such as lymphocytic infiltration, scar tissue, etc.

The importance of Wolfer's[12] experiments, showing that in dogs a cholecystitis (which is demonstrable months after its initial production) may be induced by pancreatic juice, has not been adequately recognized in the pathogenesis of cholecystitis. Wolfer found experimentally that an appreciable portion of pancreatic juice injected into the common duct or allowed to enter the common duct by a reflux resulting from mechanical intubation of the two ducts, so that a common channel was established, could be found later in the gall bladder. In either case a definite cholecystitis would result, presumably produced by the irritative action of the pancreatic secretion. It has been shown by numerous observers that the secretory pressure of the pancreas is greater than that of the liver. One can readily see then that in the human being any obstruction at this sphincter of Oddi distal to the junction of the choledochus and the duct of Wirsung, regardless of whether it was produced by stone or spasm, might allow the entrance of pancreatic secretion into the common duct and gall bladder with subsequent production of a cholecystitis.

In a small percentage of people there is such a significant variation in the size and course of the cystic duct that the slightest edema or scarring at this point would lead to serious obstruction to the inflow and outflow of bile, the latter of which is perhaps of more importance from the standpoint of production of symptoms. The actual importance of noncalculous cholecystitis becomes more obvious when we consider the suggestions of Andrews, Phemister, and others that, in general, cholesterol stones are produced by short periods of obstruction at the cystic duct and calcium stones produced by long periods of obstruction. Obviously the primary factor under these circumstances would have to be noncalculous in origin.

Although, as a general rule, the patients with calculous cholecystitis are apt to complain of more severe symptoms than patients with noncalculous cholecystitis, experience has taught us that in many instances the manifestations may be so similar that a differentiation on pure

clinical grounds is impossible. This difficulty is particularly significant if an obstruction is present at the cystic duct.

3. *Lesions of the Cystic Duct.*—When deformities of the cystic duct were emphasized many years ago as being important factors in the pathogenesis of gall bladder disease (Schmieden and Rohde[13] and Seelig[14]), the theory was accepted quite wholeheartedly, particularly in noncalculous cholecystitis. However, detailed study showed fallacies in such an explanation in a large percentage of cases. During recent years the pendulum of thought is swinging far over to the theory that dysfunction or spasm of the sphincter (biliary dyskinesia) will explain the pathogenesis in the entire group of noncalculous gall bladder disease. I am willing to accept the theory of biliary dyskinesia, but for several reasons I wish decisively to issue caution in attempting to explain the vast majority of cases of noncalculous disease on this theory. A wholehearted acceptance of biliary dyskinesia as the explanation of pathogenesis of noncalculous cholecystitis would preclude the acceptance of the data advanced during the past three or four years, that obstruction of the cystic duct is a very important primary factor in the formation of gallstones. This feature in the pathogenesis of gallstones seems to have too much foundation to allow total discredit. Last, on many occasions obstruction to the cystic duct may be unmistakable and may even be so severe as to produce a complete obstruction. Since adhesions surrounding a structure as large as an intestine can produce obstruction, why could not adhesions, which are frequently so dense about the cystic duct as to require sharp dissection, likewise cause obstruction to a lumen which is many times smaller?

Caution also must be exercised in applying the theory of cystic duct obstruction to the explanation of symptoms in a wholesale manner in gall bladder disease, but the three patients to be described appear to illustrate three of the important types of obstruction; viz., angulation of the duct, stenosis, and anomalous excessive Heisterian folds. True enough, no positive proof can be offered that lesions of the cystic duct as described in these three patients were the primary cause of the patient's complaints. Nevertheless the wall of each gall bladder was so slightly diseased and the common duct appeared so normal that we feel justified in suspecting the cystic duct as being the major factor in the production of the patient's complaints. It is quite true that two of the three patients had a pericholecystitis, which was probably secondary to previous cholecystostomy, but there is a growing tendency to attach less importance to pericholecystitis in the production of symptoms than we did a few years ago. The two patients having a previous cholecystostomy demonstrate very clearly the inefficacy of that operation. Each of the three patients whose protocols are given had an unusual amount of fat and fibrous tissue deposited about the

cystic duct, indicating that the periductal region had been the site of considerable inflammation at some previous time. Perhaps the densest periductal adhesions were encountered in Case 2, in which the stenosed cystic duct with a tiny lumen was noted.

CASE REPORTS

CASE 1.—Patient was a woman, aged 38 years; she had had a cholecystostomy performed in 1925 because of pain in the right upper quadrant and epigastrium. Symptoms were relieved up until one year before entrance to the hospital. At that time she noticed the development of a steady, gnawing pain in the epigastrium which became colicky in nature and radiated to the right upper quadrant and posteriorly. She has had numerous attacks during the past year; during the attacks of pain she was nauseated and vomited frequently. Between the attacks of pain she complained of chronic dyspepsia. For the past several months she has had pain accompanied by vomiting almost every day.

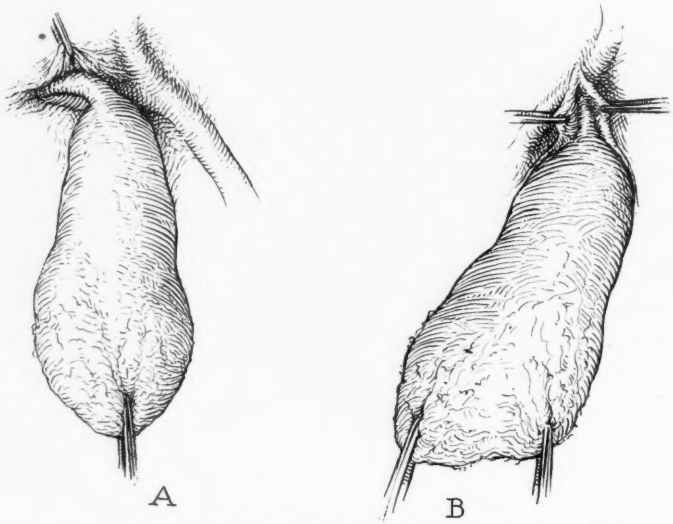

Fig. 1.—Two types of lesions at the cystic duct which are capable of creating serious interference with the proper passage of bile into and out of the gall bladder. *A*, Nothing was found at operation to explain the typical attacks of gall bladder colic (see Case 1) except the marked angulation as illustrated. The adhesions were so dense at this point that fixation must have been complete. Cholecystograms indicate that the gall bladder could fill (see Fig. 2) but could not empty properly, presumably because of the obstruction at the cystic duct. *B*, Symptoms of this patient (Case 2) were also those of a fairly typical gall bladder colic. The only operative findings which might explain the patient's symptoms were referable to the cystic duct which was stenosed and surrounded with very dense adhesions.

Examination revealed tenderness in the right upper quadrant and epigastrium of equal intensity, but no appreciable muscle spasm. The temperature was normal. The leucocyte count was 13,800. Cholecystograms revealed a shadow of almost normal density but distinctly deformed, presumably because of the previous cholecystectomy. After the fat meal the gall bladder contracted but showed a definite delay in emptying (Fig. 2). At operation the gall bladder was found to be moderately adherent to the anterior abdominal wall and surrounding organs, but the wall of the gall bladder was not thickened except at the dome, where there was a scar of a previously performed cholecystostomy. The cystic duct was buried in fatty and fibrous tissue. When it was dissected out, a sharp angulation in the cystic duct was noted. The common duct was normal in size. There were no stones in the common duct or gall bladder.

The angulation of the cystic duct in the patient described above was very pronounced (Fig. 1*A*). The valvular folds of Heister were not unusually prominent, but there was such a profuse amount of fatty and fibrous tissue deposited around this duct that the slightest edema, particularly at the point of angulation, would certainly have produced an interference with filling and emptying. The cholecystogram, as noted in Fig. 2, revealed a shadow of practically normal intensity. There was evidence of contraction after the fat meal, but emptying appeared to be definitely though not severely delayed. Delay in emptying is thought by many observers to be indicative of a definite disease process, but I am perhaps less convinced than the average observer that we can use this finding as a deciding factor indicating sufficient pathologic damage to justify cholecystectomy.

Fig. 2.—Cholecystogram of Case 1 (see Fig. 1*A*). *A*, Shadow of normal density, sixteen hours after oral administration of the dye but revealing a deformity which is presumably secondary to a previous cholecystectomy. *B*, Film taken seventy minutes after fat meal shows a slight decrease in size, but a definite retardation in emptying following the fat meal. Previous to this study, the author was inclined to minimize the significance of delayed emptying, but Cases 1 and 2 suggest that obstruction of the cystic duct may act as a mechanical factor in producing a delay in emptying.

The value of the cholecystogram in this instance is doubtful unless the delay in emptying and deformity of the shadow are considered to be indicative of a pathologic gall bladder. The patient noted that cholecystectomy had relieved her symptoms, but, as only a few months have intervened since operation, judgment on result must be deferred. The patient had typical symptoms of gall bladder colic; since operative results are so satisfactory in this group of patients, we feel quite confident that the relief from symptoms will persist.

Case 2.—Patient was a woman, aged forty-six years; she had a cholecystostomy performed one year before entrance because of pain in the right upper quadrant. For six months she was free from pain. After this interval, however, pain began

to return in attacks. Pain was moderately severe, of a colicky nature, and not associated with eating. Very little dyspepsia was noted between meals. Examination revealed tenderness in the right upper quadrant with very slight muscle spasm. The leucocyte count was 6,000. Cholecystograms revealed a distorted shadow which was less dense than normal. At operation there were numerous adhesions about the gall bladder but none of them were very dense. The gall bladder wall was not appreciably thickened. The cystic duct was buried in fatty and fibrous tissue and when dissected out was found to be unusually small, and appeared not to be patent; but examination later revealed bile in the lumen of the gall bladder. Cholecystectomy was performed. No stones were found in the gall bladder.

There is a rather marked similarity between the history, physical findings, etc., in Cases 1 and 2. In each instance the gall bladder wall was only slightly diseased, but the angulation of the cystic duct in one patient and the stenosis in the second were so pronounced that there must have been considerable obstruction to the passage of bile in and out of the gall bladder. The fatty and fibrous deposit around the cystic duct in Case 2 was so dense that the existence of acute inflammation at some previous time seemed obvious. The history of frequent attacks of pain in these two patients might support the supposition that stones were present in the gall bladder; the absence of stones supports the fallacy of attempting to predict the type of pathologic findings from the clinical findings. The most reliable data from the standpoint of predicting the type of pathology in these two patients lie in the cholecystographic findings which indicate that, although pericholecystitis exists, the wall of the gall bladder is not seriously diseased and that the cystic duct is sufficiently patent to allow passage of bile through it, although the cholecystographic shadow is less dense than normal.

Case 3.—The patient was a man, aged 37 years, who was apparently entirely well until three months before admission to hospital. At this time he noticed a steady aching pain in the epigastrium following a heavy meal. Pain did not radiate. He vomited two or three times during the first day or two. Pain lasted six days and gradually decreased. Since then he has noted that when he eats fried or greasy foods the pain reappears. Recently the pain has been relatively constant and confined to the epigastrium and right upper quadrant. Examination revealed tenderness without muscle spasm in the right upper quadrant, with a decreased amount of tenderness in the epigastrium. The temperature was normal. The leucocyte count was 9,900. Cholecystograms revealed no shadow of the gall bladder. At operation, by Dr. Puestow, the gall bladder wall was found to be only moderately thickened, with a few adhesions about the organ. Because of the absence of shadow on the cholecystogram, however, it was removed. Upon opening the gall bladder, a cup-shaped, transverse, thin, valvular fold was found in the proximal portion of the cystic duct. No stones were found.

The cup-shaped transverse valvular fold noted at the proximal portion of the cystic duct, as shown in Fig. 3*A*, was remarkably thin for a Heisterian fold but projected so far into the lumen of the cystic duct that it obviously offered definite obstruction to the duct. Ordinarily

the Heisterian folds traverse the mucosal surface of the cystic duct in a spiral fashion thereby facilitating the flow of bile. The anomalous position of a mucosal fold transversely across the lumen of the cystic duct obviously would offer a greater obstruction to the passage of bile than a spiral location. Only the proximal portion of the cystic duct was removed; we, therefore, do not know whether the remainder of the folds were anomalous or not. Even a mild inflammation of the cystic duct, with its resultant edema, would almost certainly offer serious obstruction. Such a local process, i.e., inflammation with edema and subsequent blockage of the duct, would possibly explain the attack which the patient had three months previous to admission and the

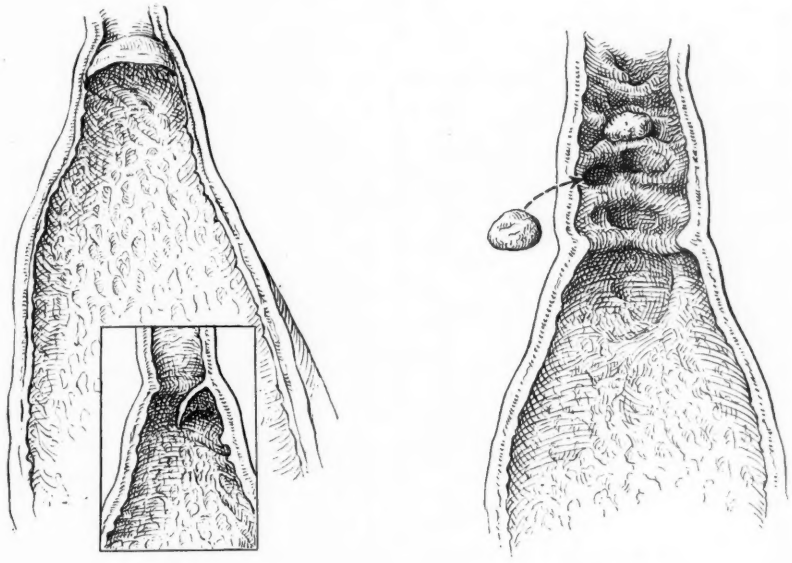

Fig. 3.—Transverse folds of Heister are anomalous and are not consistent with proper flow of bile into and out of the gall bladder, particularly the latter. *A*, Transverse cup-shaped fold found in the cystic duct of a patient (Case 3) who had symptoms for three months and whose cholecystogram revealed no shadow. It is obvious that even slight edema of the fold or wall of the cystic duct might impair exchange of bile, particularly the outflow, as illustrated more clearly by the insert. *B*, This gall bladder with transverse Heisterian folds between which two small stones were solidly imbedded is shown to illustrate perhaps a later stage in the ill effects incident to transverse folds; it is true, however, that stones may lodge in the cystic duct regardless of the configuration of the duct.

dyspeptic symptoms retained since then. The cup-shaped fold, with the concavity facing the fundus, would act as a valve and would tend to offer obstruction to emptying perhaps more readily than filling, but apparently obstructed flow in either direction, since cholecystograms showed no shadow. The wall of the fundus of the gall bladder showed so few pathologic changes that it can scarcely be blamed for the absence of a cholecystographic shadow, a finding which in our hands is quite reliable as an indication of serious gall bladder disease. Our

attention therefore is turned to the cystic duct, particularly since the common duct appeared normal and an obvious lesion was found in the cystic duct. Microscopic examination revealed a thickening and slight fibrosis of the wall of the cystic duct, but it is futile to attempt to determine how much fibrosis in a cystic duct is required to produce an obstruction with so many variable features, such as size of the lumen, thickness of bile, etc. To support the contention that a transverse fold as shown in Fig. 3*A* may be a potential source of serious difficulty, a drawing of another gall bladder with two small stones lodged between transverse folds in a cystic duct is shown in Fig. 3*B*.

4. *Biliary Dyskinesia.*—As already stated, if the theory of biliary dyskinesia as popularized by Westphal[15] and supported by the work of Ivy,[16] Newman,[17] and others is accepted as a clinical fact, it would offer a satisfactory explanation for the symptoms produced in a large percentage of patients with noncalculous "cholecystitis." Under normal circumstances the secretory pressure of bile by the liver, which varies between 300 and 360 mm. of water (Judd and Mann[18]), is far above the 100 mm. water (experimental in dogs) necessary to break through the sphincter of Oddi (Cole,[19] 1925). Although there is usually a fairly complete paralysis of the sphincter following cholecystectomy (Puestow[20]), occasional instances have been reported (Walters and associates,[21] Doubilet and Colp[22]) when sufficient spasm of the sphincter of Oddi has been noted postoperatively to produce symptoms and to require a pressure of 160 mm. of water to break through it. In such instances, the pain complained of is similar or identical to that noted before operation. Nitroglycerin (glyceryl trinitrate) relieves the pain[21] produced by this spasm.

Ivy and associates[23] have recorded some experimental findings on human subjects which support the existence of spasm of the sphincter of Oddi and its relation to distress in the right upper quadrant. During the process of draining the bile from a human subject by means of a duodenal tube, distress in the right hypochondrium was experienced simultaneously with cessation of drainage of bile. This distress in the right hypochondrium was increased by the injection of secretin-cholecystokinin, and was relieved by the introduction of magnesium sulfate through the tube. It is obviously important to find out what physiologic or pathologic factors are capable of producing spasm of the sphincter and what relation the spasm has to the production of symptoms. Walters and associates have observed that the rise in pressure within the common duct from 0 to 200 to 350 mm. water, as produced by the hypodermic injection of morphine, may at times be associated with pain in the upper abdomen. This pain and discomfort is not unlike that experienced by many patients with supposed gall bladder disease. Boyden[24] recently has shown that the sphincter cho-

lecochus is separate from the duodenal musculature and is of sufficient size that hypertrophy or overstimulation might be capable of giving rise to biliary stasis.

At the present time there is considerable discussion as to what group of patients can be classified as belonging to the syndrome of biliary dyskinesia. Part of the difficulty and confusion is readily explained if we accept Westphal's classification into two types: (1) cases in which the vagus is oversensitive (parasympathetic predominance), resulting in hypermotility or hypertonicity with rapid emptying of the gall bladder accompanied by spasm of the ampulla of Vater; and (2) cases in which the vagus is undersensitive (sympathetic predominance), creating atony of the gall bladder and ampulla with spasm of the sphincter of Oddi. However, in each type the final important disturbance is blockage of bile flow. Although it appears that the paralysis of the sphincter of Oddi as noted after cholecystectomy is usually permanent (Puestow[25]), instances have been reported, as mentioned previously, when a spasm of the sphincter of Oddi was noted postoperatively. It is apparent that this spasm may be responsible for the patient's symptoms and failure to obtain relief. It is barely possible that in many instances relief of symptoms following operation (cholecystectomy) is dependent upon a paralysis of the sphincter of Oddi. It appears that this group of patients who have persistent symptoms following cholecystectomy and in whom spasm of the sphincter is demonstrable may be classified in the group of biliary dyskinesia.

Newman[17] has classified the cases clinically into two groups. To those having spastic distention of the gall bladder he ascribes symptoms of "pain, of a dull grinding character coming on in spasms like colic but not so severe, and lasting for many minutes at a time." This pain may spread across the abdomen to the left or radiate backward on the right. A feeling of fullness, nausea, anorexia, occasional vomiting may be complained of. The gall bladder is able to concentrate normally but empties slowly. In the group having atonic distention, Newman classifies patients usually thin in stature, complaining of continuous not spasmodic pain coming on soon after meals and radiating all over the epigastrium but not to the back. Anorexia is present along with occasional vomiting but little nausea. Cholecystography "shows a very long thin gall bladder, which throws a poor shadow and empties very little." In the spastic distention type Newman reports favorable success in treatment with diet and belladonna, but he reports poor success in the atonic distention type.

5. *Metabolic Disturbances in the Biliary System.*—It seems likely that most of the pathologic metabolic findings are of importance chiefly in relation to the ultimate production of stones or to the deposition

of calcium in the wall of the gall bladder. Fowweather and Collinson[26] and Ravdin and associates[27] have noted that in hydrops of the gall bladder a high concentration of calcium was demonstrable in the contents of the gall bladder. Phemister and associates[28] have emphasized the relationship of chronic obstruction of the cystic duct to the formation of calcium stones and the deposition of calcium in the gall bladder wall. Although in Phemister's series the obstruction in the cystic duct was found to be produced by a stone, other observers have reported the association of calcium stones with obstruction of the cystic duct produced by fibrosis. It appears likely, however, that the metabolic disturbances associated with the formation of the stones as noted above were secondary perhaps to an obstruction at the cystic duct. This obstruction, which of necessity must be of a chronic nature, may be due to scar tissue produced by inflammation or due to anomalous valvular folds which might likewise produce obstruction, particularly if the cystic duct becomes involved in any inflammatory process.

The importance of the change in the bile salt-cholesterol ratio in the etiology of cholesterol stones has been emphasized by Andrews and associates.[29]

When we take into consideration the fact that a very slight increase in the concentration of bile salts in bile may produce an acute cholecystitis experimentally (Andrews), we can readily see that metabolic disturbances may be extremely important in the development of acute and chronic cholecystitis. It is probable that there are many more such metabolic disturbances which are important in the pathogenesis of cholecystitis and that they unfortunately are not as simple as this one mechanism.

6. *Cholesterosis.*—As stated previously there is a growing disbelief in the relationship[9, 30] between cholesterosis and symptoms of gall bladder disease. In the first place the condition is encountered frequently in animals (particularly the dog) in which no other manifestations of gall bladder disease are noted. Moreover, it is seen frequently at the autopsy table in patients who had no manifestations of gall bladder disease during life, implying that its appearance in the presence of definite pathologic lesions in the gall bladder or biliary tract may be of little significance. Gallstones will be found to accompany cholesterosis in one-third to one-half of the occasions when it is noted at the operating table. It is quite true that the results of cholecystectomy in such instances are very satisfactory, but it is particularly noteworthy that excision of the gall bladder in the presence of cholesterosis without stones is accompanied by poor results. Considering the above data, it is therefore doubtful if cholesterosis has anything to do with the production of manifestations attributable to disease of the gall bladder.

SUMMARY

During the past several years, a few rather radical changes in our ideas relative to the pathogenesis of gall bladder disease and the mechanism of production of symptoms have been developed. The theory of production of certain types of gallstones by obstruction of the cystic duct, the theory of production of acute inflammation of the gall bladder by chemical means, and the supposition that biliary dyskinesia is responsible for the pain in many cases of so-called cholecystitis are the three most important developments in this regard. When the possibility of production of gall bladder disease by obstruction of the cystic duct was introduced many years ago, it received wholehearted support, but some observers have ventured to entirely discredit this possibility. I contend that there are many cases of so-called cholecystitis which are dependent upon obstruction of the cystic duct for the manifestations produced and that this theory in the pathogenesis of gall bladder disease by no means can be dropped entirely. Severe angulation, stenosis of the duct and anomalous valvular folds seem to be capable of producing symptoms which are so serious as to demand relief.

It appears that biliary dyskinesia may explain symptoms in a few patients with manifestations of cholecystitis, particularly in the group which does not obtain relief following cholecystectomy. According to present reports, some of these patients complain of severe symptoms described as gall bladder colic; whereas, others complain of mild symptoms, such as dyspepsia, etc. Part of this confusion no doubt is due to the fact that the term is used too inclusively. There is scarcely any doubt that spasm of the sphincter of Oddi, when it does exist, occurs much more frequently as an entity secondary to stones in the common duct, pancreatitis, or some other organic lesion, than it does as a spasm primarily of neuromuscular origin. Extreme caution must therefore be exercised lest too much attention is directed therapeutically to relieving the spasm rather than to treatment of the lesion responsible for the spasm.

For the time being it would appear appropriate to reserve the diagnosis of biliary dyskinesia for a small group of cases, utilizing the diagnosis and therapeutic procedures advocated by Walters, Best and Hicken,[31] and others. It appears logical to assume that no single factor is responsible for cholecystitis. Many factors, including acute and chronic infection of the gall bladder, chemical inflammation, obstruction of the cystic duct, biliary dyskinesia, and perhaps others, are important in the pathogenesis of gall bladder disease.

At the present time it is practically impossible to differentiate patients with cholecystic manifestations so accurately as to eliminate

entirely surgical failures by declining operative procedures in the proper cases. One of the most common sources of surgical failure, and perhaps the most easily remedied, is the large group of patients in whom the diagnosis is grossly erroneous; i.e., the patient does not have cholecystitis but is suffering from a disease, such as carcinoma of the colon, arthritis of the spine, colitis, etc. In addition we must constantly bear in mind the fact that gall bladder disease may be present, though silent, and that the symptoms produced by the disease actually responsible for the patient's complaints may resemble those of gall bladder disease so closely that differentiation is extremely difficult. Removal of the gall bladder in these instances obviously will not relieve the patient's symptoms. In other words, all patients with gall bladder disease must be examined very thoroughly for the possible presence of another lesion in the upper abdomen or spine which may produce manifestations similar to those produced by cholecystitis. The greatest difficulty experienced at the present time in differential diagnosis lies in differentiation of patients with biliary dyskinesia and those actually having gall bladder disease. Because of the marked similarity of symptoms produced by the two conditions, it is doubtful if differentiation can be made on this basis alone. The fact still remains, however, that operation should be avoided in the group of patients complaining of only mild pain or distress and in those with doubtful cholecystographic evidence of disease.

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ROENTGEN DIAGNOSIS OF SURGICAL DISEASES OF THE LIVER AND BILIARY TRACT

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SURGICAL diagnosis owes much to the notable achievements of Wilhelm Konrad Röntgen. His discovery and the accomplishments of those who followed him have presented a method which is constantly disclosing more and more of the unknown. This applies particularly to the roentgen diagnosis of surgical diseases of the liver and biliary tract. The development of this highly important field may be divided into three periods.

The first of these eras covered about fourteen years, from the discovery of the roentgen ray to the evolution of methods for examining the stomach and duodenum by the opaque meal. During this early period, interest was centered chiefly around the demonstration of opaque gallstones in the living patient. Buxbaum[18] reported opaque gallstone shadows in 1898 and Beck[8] in this country did likewise in 1900. Results were not encouraging, however, on account of the low incidence of opaque stones.

In the second period of development indirect evidence of gall-bladder disease was demonstrated by roentgen examination of the stomach and duodenum. Schürmayer[76] is credited with directing attention to signs of inflammation in the gall-bladder region by fixation or distortion of the visualized duodenum. Those who made a careful study of the problem were even more impressed by this evidence of gall-bladder dysfunction than by the presence or absence of opaque gallstones. Nevertheless, the limitations of the method in diagnosing any abnormalities of the biliary tract were all too obvious.

The third interval, from 1923 to the present time, may well be called the era of contrast media. The outstanding feature of this period is the work of Graham and Cole.[30, 31] These men were able to demonstrate, roentgenographically, the function and the anatomy of the biliary system by means of an intravenous injection of sodium tetraiodophenolphthalein. This new method was seized upon by roentgenologists everywhere and, without doubt, now constitutes one of the most valuable procedures in the diagnosis of disease of the biliary tract.

Further assistance has been gained in the visualization of the soft tissue shadows in the abdomen by means of diagnostic pneumoperi-

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toneum. The use of halogenated oils and other opaque media to outline the biliary tract postoperatively and later the demonstration of the parenchymal shadow of the liver by the intravenous injection of thorium have increased the value of roentgen diagnosis of diseases of the liver and biliary tract.

ROENTGEN ANATOMY OF THE LIVER AND BILIARY TRACT

The position of the liver in a normal patient can be established in a posteroanterior roentgenogram of good technical quality. The liver appears as a large, homogeneous shadow in the right upper abdomen.

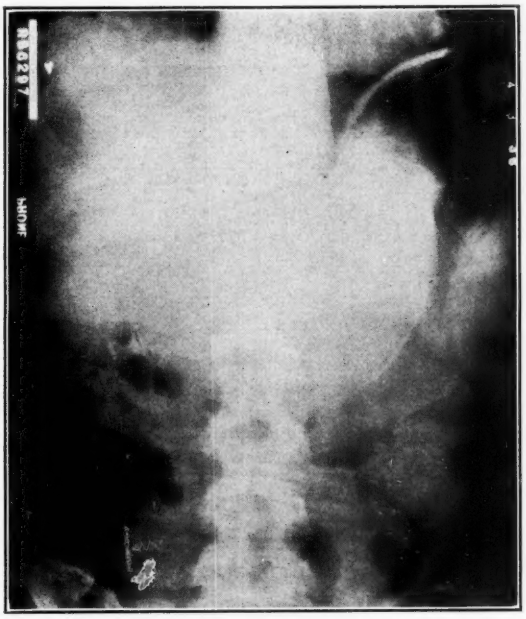


Fig. 1.—Enlarged liver. The borders of the liver are outlined by gas in the stomach and colon.

This shadow is partly superimposed by the shadows of the lower ribs. The general contour of the liver at times may be more or less outlined by shadows of gas in the stomach, duodenum, or colon (Fig. 1). The upper border of the right lobe of the liver corresponds to the dome of the diaphragm. The lower border may present two distinct lines, one conforming with the posteroinferior border and the other delineating the anteroinferior edge. The shadow of the inferior border may fade gradually into the shadow of the surrounding soft tissues without any definite line of demarcation. The right border approximates the inner aspect of the right lateral abdominal wall and frequently is not identified in its entirety. The left lobe of the liver is not readily seen because of its position in front of the spine.

In the lateral view the superior border of the liver can be seen as a curved line which is highest anteriorly. The inferior border cannot be identified with ease in this position.

The relation of the stomach, duodenum, and colon to the liver can be well demonstrated only after the use of a contrast medium. The importance of the anatomic position of these structures to that of the gall bladder is well shown by the combined use of cholecystography and the oral opaque meal (Figs. 2 and 3). Considerable variation in the relation of the structures in the right upper abdomen occurs frequently in the normal individual, depending upon body build and weight, the position of the patient at the time of roentgenography, the stage of respiration, and the amount of intra-abdominal pressure.

Fig. 2. Fig. 3.

Fig. 2.—Anatomic relations of the gall bladder, stomach, and duodenum. Prone, oblique position showing pyloric antrum, partially filled duodenal bulb, and the gall bladder in an asthenic type patient.

Fig. 3.—Anatomic relations of gall bladder, stomach, and duodenum. Prone position in hypersthenic individual.

It is well known that hypersthenic or fat persons have a high liver; whereas, the asthenic or thin patient may show a liver which is low or rotated. The liver may move from 2 to 4 cm. with normal respiration. This free mobility can be well demonstrated in films taken in the erect and supine postures.

Measurements of the liver by means of the roentgen ray have been given by Pfahler,[61] Feldman,[24] and others. The former author noted an average total vertical measurement of the right lobe as 21.3 cm., with an average anteroposterior diameter of 12.8 cm. Such figures

are of little significance in the diagnosis of disease of the liver, although marked variations in its size are of considerable importance. An interesting observation of some practical application has been pointed out by Osgood and Habbe[56] in their roentgen study of fifty-three palpable and fifty-three nonpalpable livers. They noted that, in almost all cases, the inferior margin of the liver lies at least several centimeters below the right costal margin, provided that the film is exposed on deep inspiration with the patient in the horizontal position. The palpability of the liver, therefore, depends upon other factors; namely, the firmness of its lower edge, the position of the edge in relation to the palpating fingers, and the amount of rotation which may be present. Moody and van Nuys[52] indicate that long livers, with their lower tip as much as 5.0 cm. below the interiliac line, may be normal. They found sex to be a factor in their series, with more men than women showing long livers.

Fig. 4.—Position of gall bladder in lateral view.

The gall bladder occupies a position which varies markedly in normal individuals. Such variations depend largely upon the position of the patient during the roentgen exposure, the general anatomic type of the patient, the tonus of the gall bladder, and the position of the adjacent organs. With the patient in the dorsal decubitus (supine) position, the gall bladder may lie obliquely, with the fundus directed downward and laterally, just beneath the inferior border of the liver, or it may be seen in the plane at right angles with the long axis of the spine. In the erect posture the gall bladder usually assumes a more vertical position. It may project well beyond the inferior border of the liver, with the fundus of the gall bladder well below the interiliac line. In the ventral decubitus (prone) posture the fundus may be directed obliquely downward, outward and anteriorly, in the average 150-pound patient. In fat or hypersthenic persons the fundus may be directed laterally; whereas, in thin persons it may be directed

downward and, at times, superimposed by the shadow of the vertebral column. In the lateral view the gall bladder should be well anterior to the spine (Fig. 4).

The anatomic components of the normal gall bladder can be distinguished in the cholecystogram. Occasionally it is possible to see the cystic and common duct in the cholecystogram made after the administration of a fatty meal.

DIAGNOSIS OF DISEASES OF THE LIVER

The roentgen examination may be valuable in the demonstration of many lesions involving the liver. Such assistance, however, is dependent upon certain factors which may be introduced as an aid in diagnosis or which may be present as a result of disease. These factors

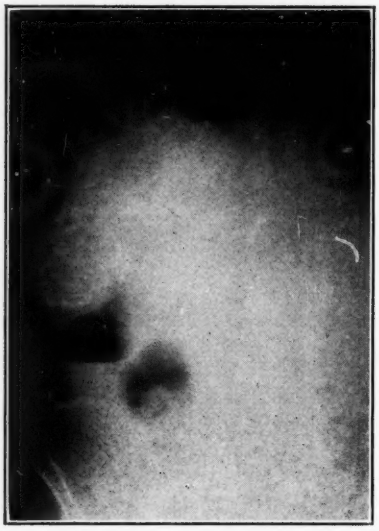


Fig. 5.—Calcification in the liver. Due to a large echinococcus cyst. (Courtesy of Dr. Herman Ostrum.)

include: (1) variations in density, such as calcification, gas shadows, fluid levels, or opaque media; and (2) variations in size, shape, or position of the liver itself or of its neighboring organs, visualized with or without opaque media.

Calcification in the liver is not common and occurs mostly as calcium carbonate and phosphate. When present, it is more often in centrally necrosed lobules, but it has been observed in Glisson's capsule in cases of nephritis.[41] Although evidence of such calcifications in the roentgenogram may not be diagnostic, they may be of considerable value in association with the anamnesis, or the clinical history, of the patient. Aimard[1] has shown a mass of calcified tubercles on the lower border of the liver mistaken for gallstones. Such calcified shadows are usually not homogeneous in density or regular in outline. They may be clumped or scattered throughout the parenchyma. In the

latter case it may be difficult to differentiate calcification from intrahepatic stones. Calcification may occur in the liver as a result of small abscesses, fungus infection (actinomycosis and blastomycosis), and parasitic infestation, such as echinococcus, pentastomum denticu-

Fig. 6.—Localized bulge of left diaphragm. Due to a tumor of the liver.

Fig. 7.—Metastatic malignancy involving the liver. Lateral view shows marked enlargement with elevation of the right dome of the diaphragm.

latum, and, rarely, cysticurcus, distoma, or psorospermia (Fig. 5). Multiple small calcifications may occur as a result of thrombosis associated with cavernous angiomas of the liver. A calcified plaque, the result of a perihepatitis, at times may be demonstrable in the roentgenogram.

Occasionally air and fluid levels in the liver can be shown, if the roentgenograms are made in the erect posture. If these shadows can be localized to the liver parenchyma, they usually indicate an abscess or cyst. Their presence indicates either a fistula or an infection by gas-forming organisms.

Lepennetier and Altman[46] have divided the supracolic hydroaerial images as follows: (1) subphrenic abscess, (2) hydatid pyopneumocysts of the liver, (3) chronic peritonitis of the hepatic flexure region or a high loop of jejunum, (4) certain forms of hepaptosis with interposition of a loop of bowel between the liver and diaphragm, and (5) images of the gastroduodenal region. Gangrenous gaseous cholecystitis is a rare condition which may produce an air-fluid level in the right upper abdomen. It may be distinguished by the presence of gaseous infiltration of the wall of the gall bladder.[78] Sometimes these air and fluid levels may be confused with subphrenic abscesses, as in the case reported by Altounyan,[4] in which a large air and fluid level was found to be due to a hydatid cyst. Gumma or other localized tumors, if near the superior surface of the liver, may cause a localized nodulation of the right dome of the diaphragm (Fig. 6). The hepar lobatum of syphilis may be distinguished by the smooth, nodular shadow of the enlarged viscus. In leukemia the liver may become enormous in size and sometimes hematogenous metastatic malignancy produces a gigantic liver (Fig. 7). Cystic disease of the liver is not common. It may be suspected when an enlarged liver is associated with pyelographic evidence of polycystic kidneys.

Liver abscess, with the exception of tropical abscesses, occurs most frequently as a result of infection transmitted through the portal system or bile ducts. Sérégé[77] has shown that there are two currents of blood in the portal vein (Fig. 8). One of these originates in the superior mesenteric vein and is distributed in the right lobe of the liver; the other, arising in the inferior mesenteric vein, finds its way chiefly to the left lobe. In our experience most liver abscesses have been associated with infection originating in the right abdomen and hence have involved the right lobe of the liver. The importance of the roentgen examination in abscess of the liver has been shown by Eliason,[23] Pancoast,[58] and Granger.[33] Careful fluoroscopic study and film examination are essential. In many cases serial examination from day to day is necessary before the diagnosis can be established. Pancoast[58] states that the roentgen evidences may not be seen before the fifth day following the onset of the abscess. Roentgen criteria of liver abscess are:

1. *Elevation of the Diaphragm.*—This may be slight or high. The contour of the diaphragm may be smooth or there may be a nodular, localized bulge. Often the costophrenic or cardiophrenic angles are clear. A sudden elevation of the right diaphragm during the course

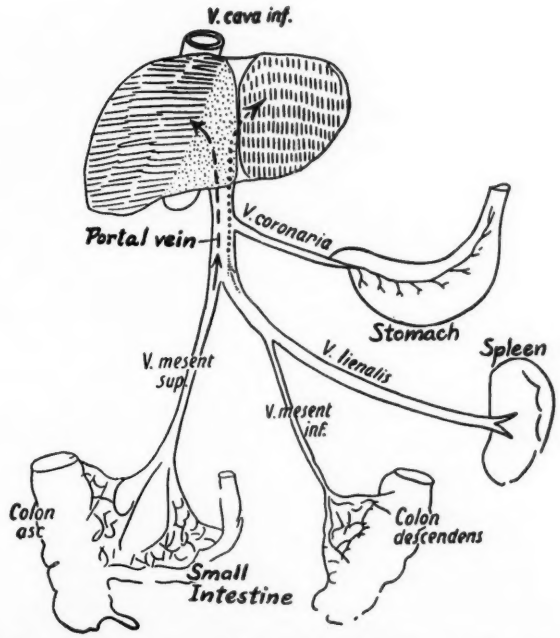


Fig. 8.—Diagram showing two currents in the portal vein. From L. Lichtwitz (Pathologie der Functionen und Regulationen, 1936) after C. Henschen.

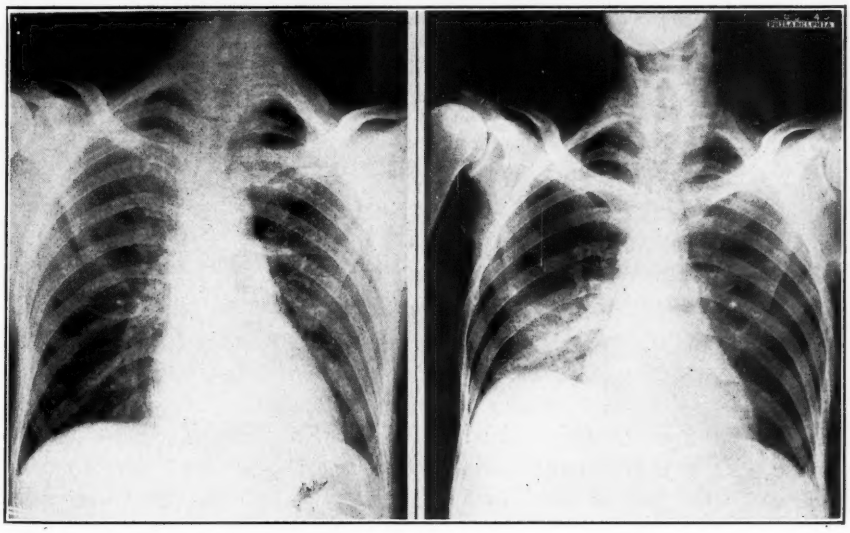


Fig. 9. Fig. 10.

Fig. 9.—Liver abscess. The right diaphragm is not elevated but shows some restriction of motion.

Fig. 10.—Liver abscess. Same patient as shown in Fig. 9, a few days later following rupture of the liver abscess. Right dome now elevated and fixed. There is a lung reaction in the right lower lobe.

of a day-to-day examination may mean rupture of a liver abscess into the subphrenic region[58] (Figs. 9 and 10).

2. *Restriction of Motion of the Diaphragm.*—According to Pancoast,[58] this may occur in spite of the situation of the liver abscess. When it is adjacent to the superior surface of the diaphragm, the restriction is apt to be more pronounced than when the abscess is deeper in the liver parenchyma. This limitation of motion is not present with tumors or gumma, which may produce localized or diffuse elevation of the diaphragm. Elevation of the diaphragm, with limitation of its respiratory excursion, also may occur as the result of operative trauma.[3] In such cases one or both domes of the diaphragm may be affected. The condition may last only a few days, and the knowledge of a recent operation avoids diagnostic confusion. Nonsuppurative cholangitis may cause some restriction in the excursion of the diaphragm, but this usually is not associated with marked elevation. Here again, the clinical findings aid in differentiating liver abscess.

3. *Lung Reaction.*—Although this is more common in association with subphrenic abscess, it may occur with liver abscess when such a lesion is near the diaphragm. It consists of a more or less hazy increase in density involving the lower right lung field and may be associated with a pleuritis and effusion. This pulmonitis and pleuritis sometimes are quite confusing, so that in spite of careful study it is not always possible to differentiate roentgenologically between a primary infectious process below the diaphragm and one above the diaphragm. In such cases great help is afforded by removing and examining the fluid from the pleural cavity. Whereas clear fluid indicates a lesion primarily below the diaphragm, purulent fluid indicates an infectious process originating in the thorax. The roentgen localization of the abscess in the liver can be made only by finding an hydroaerial image in the film made in the erect posture. Unfortunately, this is not possible in many cases.

Abscesses of the liver may rupture Glisson's capsule into the free abdominal cavity, the pleural cavity, the lungs, bronchi, pericardium, or other structures. A subdiaphragmatic abscess, occurring as a result of rupture of a liver abscess, may cause elevation and fixation of the dome of the diaphragm. Granger[33] has indicated that one can differentiate a subphrenic abscess secondary to a hepatic abscess from one secondary to a peritonitis by a study of the pleurodiaphragmatic angles. In the former type he states that the cardiophrenic angle and the anterior costophrenic angle may be obliterated; whereas, in the latter the lateral costophrenic and posterior costophrenic angles are obliterated. An air-fluid level may or may not be present in subphrenic abscess.

Abscess of the left lobe of the liver is less apt to affect the diaphragm. Miles[50] has collected eighty-five cases of abscess of the liver,

eight of which involved the left lobe. The clinical symptoms and signs may be vague and may last for a variable period of time. Such abscesses, because of their position, tend to cause downward enlargement of the liver. The roentgen diagnosis is based upon fluoroscopic examination of the barium-filled stomach and upon film examination made in the posteroanterior and lateral positions. These studies show a downward and posterior displacement of the stomach in cases where the abscess is located laterally. When the abscess is more mesial, the posterior displacement of the fundus and cardia is less. Miles[50] states that when the abscess involves the caudate lobe, the distal portion of the stomach may be displaced downward and forward. In the differential diagnosis of these abscesses it is necessary to consider other tumors which occur in this position, chiefly gumma, but also echino-

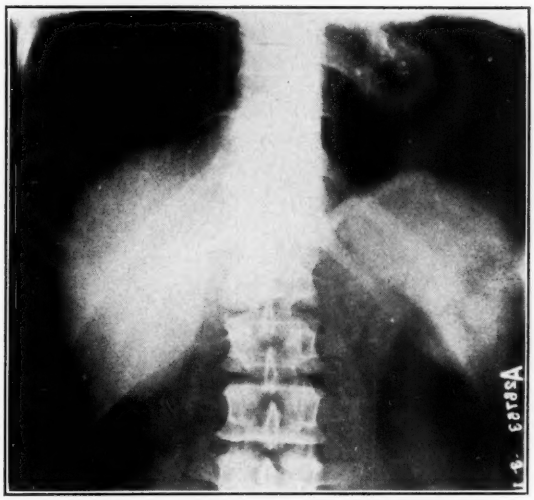


Fig. 11.—Increased density of the liver and spleen. Roentgen appearance similar to that seen after injection of thorium. This was accidentally discovered in a routine roentgenogram of the abdomen. We were unable to explain this peculiar appearance and tests showed no evidence of radioactivity. No history of previous thorium injection. Satisfactory diagnosis not available. (Courtesy of Dr. Paul Bishop.)

coccus cysts, metastatic carcinoma, hemangioma, omental cysts, retroperitoneal malignancy, and pancreatic tumors or cysts.

Thorium dioxide sol has been used in the demonstration of diseases of the liver. This radio-opaque substance has an affinity for cells of the reticuloendothelial system. When injected intravenously, it causes increased density of the liver and spleen (Fig. 11). Such increase in radio-opacity depends upon the amount and distribution of the reticuloendothelial cells. We have had no experience with this procedure. In general the use of the substance has been restricted to experimental animals and patients with incurable diseases. While there is no doubt of its value as a diagnostic procedure, there are certain dangers which accompany its use. Immediate reactions may include urticaria, skin

and mucosal hemorrhages, chills, headache, diarrhea, and asthmatic attacks. Fervers[25] has reported death immediately following injection in the human being. Rupture of the spleen or liver may occur.[17] Late reactions may be the result of the radioactive properties of thorium. Pohle and Ritchie,[65] after studying the effects of thorotrast in rabbits, recommend restriction of its use for diagnostic purposes to incurable cases. Naegeli and Lauche[54] have observed degeneration adenomas in the liver five years after the injection of thorium in the dog. Such damage, however, is not in accord with all observations and may be the result of excessive dosage. Yater and others[86] have examined 200 patients following hepatosplenography with thorium dioxide. In the dosage used by them (½ c.c. for each pound of body weight), they have had no immediate reactions during the past three years. They have noticed no ill-effects in patients now living, some as long as four years and nine months, and they have not found any damage to liver cells by histopathologic study of 71 cases. Hepatosplenography has been utilized as follows:[86] (1) To determine the nature of a mass in the upper part of the abdomen; (2) to determine the presence and kind of hepatic disease; atrophic cirrhosis, hypertrophic cirrhosis, syphilis, metastatic malignancy, primary tumor, abscess, cyst, or amyloidosis; (3) to ascertain whether metastatic lesions are present in the liver if operation is contemplated for carcinoma; (4) to demonstrate rupture of the liver or spleen; (5) to determine the cause of jaundice, whether intrahepatic or due to obstruction of the common bile duct; (6) to follow the progress of hepatic or splenic disease; (7) to demonstrate whether a lesion is above or below the diaphragm; (8) to diagnose ascites; and (9) to study diseases of the spleen.

VARIATIONS IN POSITION AND ANOMALIES OF THE LIVER

It has been pointed out that the normal liver is not a fixed organ but, within certain limits, is freely movable in the abdominal cavity. It is held in position mainly by the inferior vena cava, the coronary and suspensory ligaments, and by the pressure of surrounding viscera. It may be easily displaced by intraperitoneal air or fluid, leaving a wide space between the diaphragm and its superior and lateral surfaces. Bürger[16] has observed ten cases of partial dystopia of the liver in which there was an interposition of portions of the intestinal tract between the liver and the diaphragm or lateral abdominal wall. Distention of these loops by gas may cause pain, radiating to the back and right shoulder. In all the cases which Bürger observed, there was a stenosing parapyloric ulcer, which may have accounted for the downward and medial displacement of the liver. One of us[59] has previously called attention to interposition of gas shadows between the liver and the diaphragm, secondary to a complete dislocation of

the liver. In this case the haustral markings of the colon could be identified in the roentgenogram. The condition also may be the result of eventration of the right diaphragm[84] or a right phrenic paralysis.[79] The surgical importance of this condition can be seen illustrated in Fig. 12. Following a subtotal gastrectomy for duodenal ulcer, this patient was examined because of a suspected subdiaphragmatic abscess. The films show air and fluid levels lateral to and above the right lobe of the liver. With this evidence, a needle was inserted into the parahepatic space in an attempt to corroborate the diagnosis. A transdiaphragmatic approach then drained the abscess. At autopsy the condition proved to be an interposition of multiple loops of jejunum with a localized peritonitis and subphrenic abscess.

Fig. 12.—Hepaptosis and subphrenic abscess. Air and fluid levels represent collections in the jejunum above and lateral to the liver. (Courtesy of Dr. Karl Kornblum.)

Congenital anomalies of the liver are not common. Complete situs transversus is not difficult to diagnose in the roentgenogram, if one looks for it. Transverse furrows may sometimes be identified by the uneven appearance of the right dome of the diaphragm. Riedel's lobe may be readily demonstrable in the properly exposed roentgenogram, but it may be missed if careful roentgen technique is not carried out or if the individual be muscular or obese. Multiple lobulations, isolated accessory lobes, or attachment of the left lobe to the spleen is usually not shown in the routine roentgenogram of the abdomen.

Anomalies in size of the liver may occur as a diminution in the right or left lobe or as an increase in the size of any of the four lobes. We

have had the opportunity to observe one case of anomalous enlargement of the right lobe of the liver.[44] In the lateral roentgenogram of the chest and diaphragm the shadow of the enlarged liver, superimposed on the cardiac shadow, produced an image which was mistaken for an interlobar collection of fluid between the right middle and lower lobes (Figs. 13 and 14). At autopsy, a huge right lobe of the liver had elevated the diaphragm to the level of the second anterior interspace.

THE GALL BLADDER

The function of the gall bladder is to receive, store, and concentrate bile delivered to it through the biliary system from the liver cells. It also may equalize the pressure in the biliary system and periodically

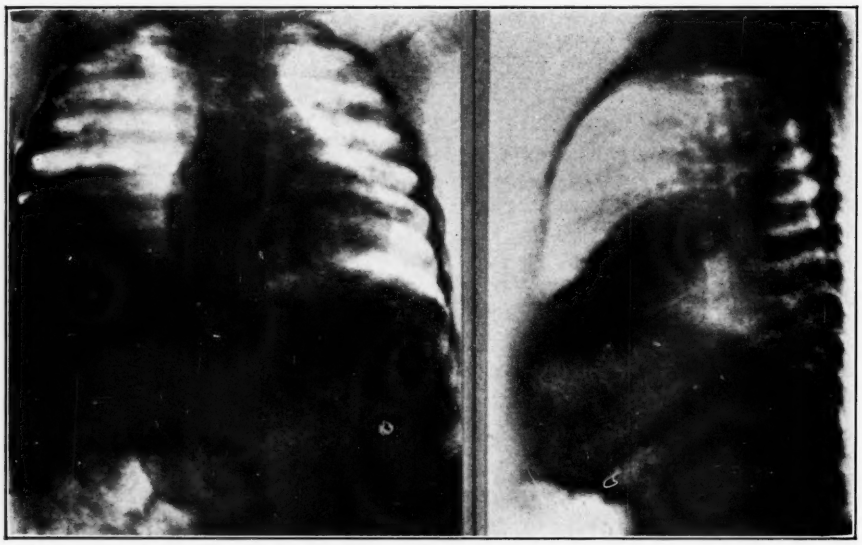


Fig. 13.—Anomalous enlargement of the right lobe of the liver. In the lateral view the appearance simulates an interlobar collection of fluid. (Case previously reported by Dr. Kornblum and Dr. Stephenson, Am. J. Roentgenol. 24: 38, 1930.)

deliver bile into the duodenum.[55] The principal physiologic properties of the gall bladder are absorption, secretion, and motor activity. By virtue of these properties, Graham and Cole[30, 31] developed a roentgenographic test of gall-bladder function. In 1924 they produced successful roentgenograms of the gall bladder by the use of sodium or calcium salts of tetraiodophenolphthalein and tetrabromphenolphthalein. Ivy,[39] Ravdin and co-workers,[67] and others have shown that the gall bladder may concentrate hepatic bile as much as six to seventeen times. This concentration depends upon the absorption of water from the gall-bladder contents. When absorption occurs, it creates sufficient concentration of the sodium tetraiodophenolphthalein to permit visualization of the gall-bladder shadow in the roentgenogram. Failure to

see the gall bladder after the proper administration of sodium tetraiodophenolphthalein may be due to: (1) damage to the gall-bladder wall, (2) inability of the liver cells to excrete the dye, (3) obstruction of the cystic duct, (4) incompetency of the mechanism of the sphincter of Oddi, and (5) certain conditions which may be present outside of the biliary tract and which may interfere with the absorption, secretion, or concentration of the dye.

Indications for this test are obvious. While it is primarily a demonstration of functional activity, it is, also, of great value in the determination of any anatomic deformity. Contraindications to the method are few. Graham and others[32] mention cardiac decompensation and threatened uremia as contraindications to the injection of sodium tetraiodophenolphthalein. We have not hesitated to use it orally in such conditions. Although we do not advocate the promiscuous use

Fig. 14.—Deformed gall bladder, due to pressure from an enlarged liver.

of the drug in patients with severe liver damage or with obstruction of the common duct, we do not believe that such are definite contraindications in all cases. The use of the procedure is limited in obstructive jaundice because: (1) the examination has not proved of value in demonstrating the gall bladder, (2) the use of the drug may cause pancreatitis, when there is an obstruction in the common duct near the duodenum, and (3) further damage to already damaged or impaired liver cells may occur.[69] Rudisill,[72] however, has demonstrated the gall bladder roentgenographically in seven of eight cases of catarrhal jaundice and we have made at least one similar observation.

Iodism or allergic reactions are uncommon following the use of sodium tetraiodophenolphthalein. Reactions to the intravenous injection also are uncommon but may be more severe than when the dye is given orally. Following injection, the patient may complain of nausea, vomiting, chills, circulatory depression, fever, and abdominal cramps of varying degrees of intensity.[21] Orally the drug may cause

nausea, vomiting, diarrhea, and abdominal cramps of severe or mild degree. Skin reactions may occur and are usually mild.

TECHNIQUE OF DYE ADMINISTRATION

It is desirable to expose a film of the gall-bladder region before the sodium tetraiodophenolphthalein is given. This is routine in some laboratories, but we have not used it because: (1) many of our patients have a gastrointestinal examination or urographic studies which serve the same purpose, (2) one more day is added to the usual two-day examination.

It has been our custom to use the oral method of dye administration as a routine procedure. Occasionally, when vomiting is severe or pyloric stenosis is present, we give the dye by intravenous injection. Sandström,[74] in 1931, and Stewart and Illick,[81] in 1935, advised fractionating and increasing the peroral dosage on the basis that this procedure produces a cumulative effect in the contrast filling of the gall bladder. We have used a modification of the intensified technique outlined by Golden.[28] Briefly this consists of the ingestion of 60 gr. of pure sodium tetraiodophenolphthalein immediately after a "low fat" noonday meal, the day previous to the roentgen examination. This dose is repeated on the same day following a similar evening meal. The patient reports to the department the next morning, twenty-one hours after the first—14 hours after the second—dose of the dye has been taken. We make no effort to administer excessive carbohydrate, other than that which the patient may receive as the result of the low fat meals. Total abstinence from food or water is required after the last dose of the drug. One dram of tincture of opium is given one-half hour after each dose of the dye.

When the intravenous injection is preferable, we use 40 mg. of sodium tetraiodophenolphthalein per kilogram of body weight. The drug, diluted with normal saline solution, is injected by gravity, through carefully sterilized glassware and tubing. The injection is given the evening before the film examination and the patient is kept on a fasting diet in the interim. Certain writers[83] have pointed out that it is possible to make simultaneous tests of liver function by the use of the intravenous method of giving the dye.

Other methods of administering the dye have been used. A rapid method of cholecystography has been outlined by Antonucci.[6] By first placing the patient on a low carbohydrate diet for a few days and then injecting 125 c.c. of 40 per cent glucose solution immediately preceding the injection of 2 or 3 gm. of dye, the gall bladder may be visualized in one-half hour and reaches maximum opacity in two hours. Milani[49] states that one can differentiate the normal gall bladder from the strawberry gall bladder by this method. In the latter cases the gall bladder is not seen before two hours following the injection of the dye.

ROENTGEN TECHNIQUE

The first film made is a large one (14 by 17) to include the entire abdomen. We have found this extremely useful in diagnosing many abdominal conditions which otherwise would be missed. The film is intended to locate the gall bladder and to determine the size of the liver. In addition we have found diaphragmatic hernia, calcified abdominal aneurysms, calcified lymph nodes, calcified adrenals, cold abscess, subphrenic abscess, calcifications in the kidneys, calcifications in the spleen and liver, myocardial aneurysm, and situs transversus. Our second film (10 by 12) is exposed immediately after the first and is centered over the gall-bladder region with the patient slightly rotated (20 to 30°), so that the right side is away from the examining table. These two films are developed at once and viewed. If they are satisfactory, the fatty meal is given without delay; otherwise, more films are exposed as indicated. We have found the use of pitressin valuable in eliminating gas shadows and contents in the hepatic flexure which interfere with visualization of the gall bladder. A cleansing enema also can be used for this purpose. The last film is made one-half hour after the fatty meal has been eaten. Under some circumstances, such as lack of gall-bladder contraction, more films may be exposed to determine the approximate emptying time of the gall bladder.

NOMENCLATURE AND INTERPRETATION OF ROENTGENOGRAMS

In 1935 one of us[60] pointed out that the radiologist has no right to make a diagnosis of normal functioning or nonfunctioning gall bladder from the roentgenograms and therefore offered the following nomenclature for reporting the results of cholecystographic studies.

A. *Functioning Gall Bladder.*—Such an interpretation would include those gall bladders which showed good concentration of the dye and good emptying after the fatty meal.

1. *Functioning gall bladder with stones:* Such an interpretation would include those gall bladders which showed good concentration and good emptying, but in which stones could be identified.

2. *Functioning gall bladder with mural growth (papilloma):* Such an interpretation would include those gall bladders with good concentration and emptying but in which, after changing position, the filling defect remained constantly in the same location.

3. *Functioning gall bladder with adhesions:* Such an interpretation would include gall bladders that showed good concentration and emptying but which, due to their peculiar contour or location, indicated pericolic adhesions. This diagnosis is difficult but is included to make the classification complete.

4. *Functioning gall bladder with anomalies.*

B. *Partially Functioning Gall Bladder.*—Such an interpretation would include those gall bladders which did not show adequate dye concentration or ability to empty properly, or which became larger after the fatty meal.

1. *Partially functioning gall bladder with stones:* Such an interpretation would include those gall bladders which did not show adequate dye concentration or emptying and in which gallstones could be identified.

2. *Partially functioning gall bladder with anomalies.*

C. *Abnormally Functioning Gall Bladder.*—Such an interpretation would include those cases in which there was very poor or no gall-bladder visualization or those in which the gall bladder increased in size during the examination, thereby indicating a reversal of flow.

1. *Abnormally functioning gall bladder with stones:* Such an interpretation would include those cases in which there was very poor or no gall-bladder visualization, but in which opaque calculi could be seen. Stones could be classified as "nonopaque" and "opaque."

2. *Milk of calcium bile.*

3. *Calcified gall bladder.*

4. *Abnormally functioning gall bladder with anomalies.*

Noncalculous Cholecystitis.—This disease may produce a dense, faint, or absent gall-bladder shadow in the cholecystogram. The density of the dye shadow varies with the amount of damage to the gall-bladder wall.[20, 39] The function of the gall bladder may return to normal, as indicated by cholecystography, followng major or minor inflammatory changes to its wall.[27, 40] This may account for the fact that the pathologically abnormal gall bladder has shown what we would term "functioning gallbladder," by the cholecystographic test. Hodges and Lampe[37] encountered a 16 per cent error in this respect. They have also noted that among twenty-one patients with proved major inflammatory disease of the gall bladder, 95 per cent showed faint visualization or no shadow in the roentgenogram. Whether the pathologic evidence or the roentgen evidence is the proper criteria in relation to the clinical symptoms is undecided. Suffice to say that a fairly large percentage of patients who have had a cholecystectomy for noncalculous cholecystitis are not relieved of their symptoms. Ravdin[68] put this even more forcefully when he stated: "It is very likely that in well over half of the operated cases, the gallbladder does not account for the patient's symptoms."

Adhesions.—There are some writers who try to interpret anatomic deformity or motor disturbance in terms of pericholecystic adhesions. We believe that the roentgenologist who attempts such interpretations, in many cases, is treading on thin ice. Our experience has included roentgenologically deformed gall bladders which were entirely normal and without adhesions at operation, and roentgenologically normally

shaped gall bladders which at operation were bound down or deformed by extensive pericholecystic fibrous changes. Fig. 14 shows a deformity which is due to pressure from an enlarged liver.

Fig. 15.—Opaque gallstones. The faint shadow of a partially functioning gall bladder can be seen.

Fig. 16.—Irregular calcification in cold abscess. Gall-bladder shadow can be seen above the cold abscess.

Calculous Cholecystitis.—The roentgenographic shadow cast by an opaque gallstone depends not only on its total calcium contents but particularly on the distribution of the calcium in the stone.[70] It is probably true that less than one-third of all gallstones are radio-opaque (Fig. 15). A discussion of the etiology of gallstones will be avoided,

except to state that two factors may play an important role. The first of these is obstruction; the second, inflammatory changes in the gall-bladder wall.[5, 35, 62] Occasionally we have noticed a stone which has a layer of calcium on only one portion of its periphery. This we

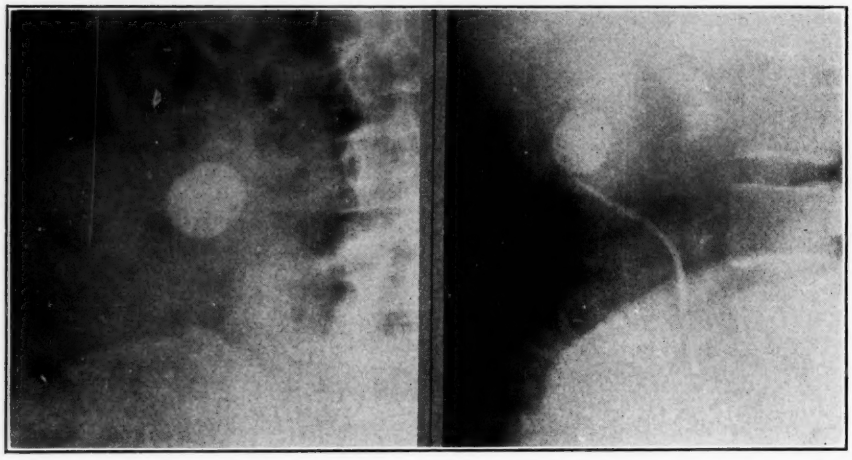


Fig. 17. Fig. 18.

Fig. 17.—Large dense shadow in the right abdomen. Thought to be due to calculus in the gall bladder.

Fig. 18.—Lateral view, same patient as shown in Fig. 17. Opaque catheter in ureter shows the shadow to be due to a renal calculus. Note the anterior position of the calculus in relation to the spine. This sometimes occurs when the kidney is enlarged.

Fig. 19.—Calculus cholecystitis. The gall-bladder shadow is quite dense, but there is a single, large, nonopaque stone in the fundus. At operation, a typical "strawberry gall bladder" containing a stone was removed.

have attributed to the fact that at one time or another this stone has obstructed the cystic duct. The associated inflammatory changes in the gall bladder have resulted in the deposition of calcium on the exposed side of the calculus.

Differential Diagnosis of Opaque Calculi in the Right Upper Abdomen.—The most common opaque shadows in this region, which may be confused with gallstones, are: renal calculi, calcified glands or vessels, opaque shadows in the gastrointestinal tract (barium in diverticula of the colon), calcification in the liver or pancreas, and calcification in a tuberculous abscess (Fig. 16). Careful and often repeated roentgeno-

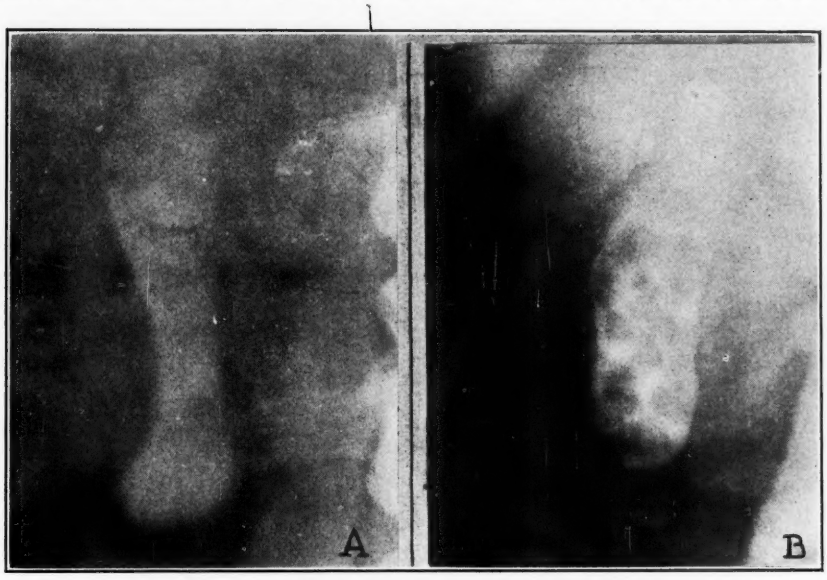


Fig. 20.—Nonopaque gallstones, developed in twenty-six months.

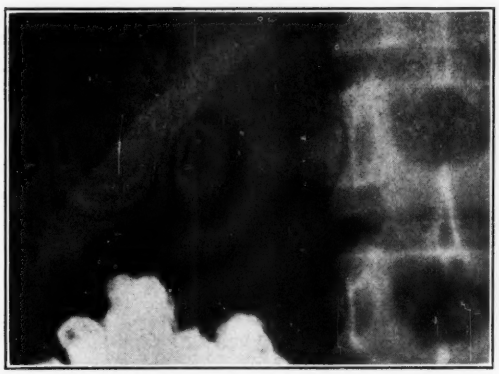


Fig. 21.—Gas shadows in the duodenum. Such shadows may be confused with nonopaque gallstones.

graphic or roentgenoscopic examinations, with the patient in various postures, frequently are necessary for correct interpretation. Pyelography may be required to exclude renal calculi (Figs. 17 and 18). Moles or small tumors on the patient's skin, particularly if they are in a position where they are pressed against the film or examining table, may produce a round, dense shadow in the roentgenogram.

Following the use of the Graham-Cole test, the gall bladder involved by calculous cholecystitis may be dense, faint, or not visualized. The detection of nonopaque stones in the roentgenogram depends upon the presence of contrast substance (Fig. 19). Fig. 20 shows multiple nonopaque stones which have developed in a period of twenty-six months. Nonopaque stones may be confused with gas in the intestine (Fig. 21). Akerlund[2] and others have demonstrated stratification or layers of bile in films made in the erect posture. In five of Akerlund's cases nonopaque stones could be demonstrated as filling defect between the layers of different density. Kirklin[42] was able to diagnose gallstones as such in 70.8 per cent of the cases examined. He found, however, that in a group of 415 patients having gallstones at operation, 99 per cent showed abnormal cholecystographic findings. Our own observations have led us to an absolute diagnosis of stones in only 27 per cent of patients in whom stones were found at operation. We have been inclined toward conservatism in this respect, because we feel that the danger seems to be in interpreting too much, rather than not enough, in patients with abnormal gall-bladder function. Hodges and Lampe[37] have summarized the situation in their study of 121 cases of proved calculous cholecystitis.

NO. CASES		ROENTGEN DIAGNOSIS OF STONES	
88	No dye shadow	28	32%
33	Dye shadow	31	94%
121	All cases	59	49%

These investigators write: "It is noteworthy that normal visualization without stones was never reported in the case of patients later shown to harbor calculi."

A comparison of the value of cholecystography and biliary drainage in the diagnosis of gallstones has been presented by Bockus and others.[10] Biliary drainage was accurate in diagnosing or excluding gall-bladder pathology in 98 per cent of 148 cases; whereas, in this same group cholecystography gave an accurate diagnosis in 88.4 per cent. In cholelithiasis alone biliary drainage indicated stones in 83.2 per cent of their cases, as against 29.2 per cent by cholecystography. Biliary drainage, however, is satisfactory only when "B" bile is obtained and its efficacy in the diagnosis of stones depends upon the skill of the observer. For these reasons, the authors conclude that, if one study only is to be carried out, it should be intravenous cholecystography. Miller[51] has found duodenal drainage indicative of stone or lack of function in 91 per cent of stone cases, while cholecystography revealed stone or lack of function in 87 per cent of these patients.

Milk of calcium bile is a term which has been used to indicate deposits of opaque material, chiefly calcium carbonate, in the gall bladder. This condition has been adequately described by Churchman,[19]

Kornblum and Hall,[45] Phemister and others.[63] Prior to operation, the roentgen examination is the only means of establishing this diagnosis. Roentgen diagnosis is contingent upon the finding of a dense gall-bladder shadow, which may be homogeneous or mottled, depending upon the amount of nonopaque detritus present. The gall-bladder is sometimes small and shrunken and does not empty after the fatty meal (Fig. 22). Often, an opaque calculus can be seen in the region of the cystic duct. Films made in the erect posture may demonstrate partly calcified debris in the fundus of the gall bladder, above which there is a homogeneous shadow of lesser density (Fig. 23). When the condition is suspected, films should be exposed without the administration of gall-bladder dye.

Calcification of the gall-bladder wall or porcelain gall bladder has been described by Blatter[9] and others. This condition may be confused with a dye-containing viscus, milk of calcium bile, or calcified

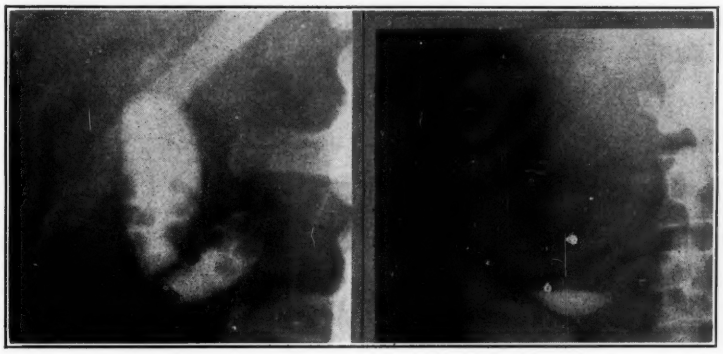


Fig. 22. Fig. 23.

Fig. 22.—Milk of calcium bile and nonopaque gallstones. There is no change in the size or shape after the fatty meal. Putty-like material, mixed with cholesterin stones, was found at operation.

Fig. 23.—Milk of calcium bile. Erect film showing fluid level in the gall bladder. At operation, a thin, milky fluid was found, associated with a small amount of detritus and a few small, nonopaque stones.

gallstone. It may present, however, a characteristic streaked or mottled appearance which does not vary with the position of the patient (Fig. 24).

Tumors of the gall bladder have been uncommon in our experience. Statistics indicate that primary carcinoma of the gall bladder may be found among 5 to 7 per cent of all carcinomas found at autopsy. Malignant lesions are apt to produce an early occlusion of the outlet of the gall bladder and, hence, do not lend themselves to visualization by cholecystography. Our observation concurs with that of other writers, that this most important group of tumors of the gall bladder has not been diagnosed by cholecystography, except in rare instances. They are frequently associated with gallstones, however. Wilkie[85] has had thirty-one cases of carcinoma of the gall bladder, all of which had associated biliary calculi.

Benign tumors of the gall bladder may be demonstrated by cholecystography. The roentgen diagnosis of these conditions has been excellently presented by Kirklin[43] and by Moore.[53] Papillomas are usually small, not exceeding 1 cm. in diameter. They may be single or multiple. Frequently the gall bladder shows no other changes, although there may be an associated chronic cholecystitis or cholelithiasis. The roentgen diagnosis depends upon the finding of one (or more) clear, oval, or circular defect which remains constant with changes in the position of the patient (Fig. 25). Such a defect will always be adjacent to the gall-bladder wall. These shadows are most apt to be seen in those films made during evacuation of the opaque dye from the gall bladder. Not infrequently the gall-bladder shadow is denser than average. Cholesterol stones may be differentiated by

Fig. 24.

Fig. 25.

Fig. 24.—Calcification of the gall bladder. Roentgenogram made after removal shows the irregular flakes of calcification in the wall of the viscus.

Fig. 25.—Papilloma of the gall bladder. The small defect can be seen near the superior surface in the body of the gall bladder. The gall-bladder shadow is quite dense.

their tendency to change position in their relation to the gall-bladder wall, by their angular outline, or by the presence of calcium deposit.

Adenomas most often occur in the fundus of the gall bladder. They may be larger than the papillomas. The gall-bladder shadow may be dense or faint. Like the papillomas, the adenomas are more easily detected roentgenologically in films made during the emptying phase of the gall-bladder function.

EMPTYING OF THE GALL BLADDER

Many investigators have shown that the gall bladder contracts, in response to certain stimuli, to empty its contents into the cystic and common ducts. As yet there is no agreement among radiologists as

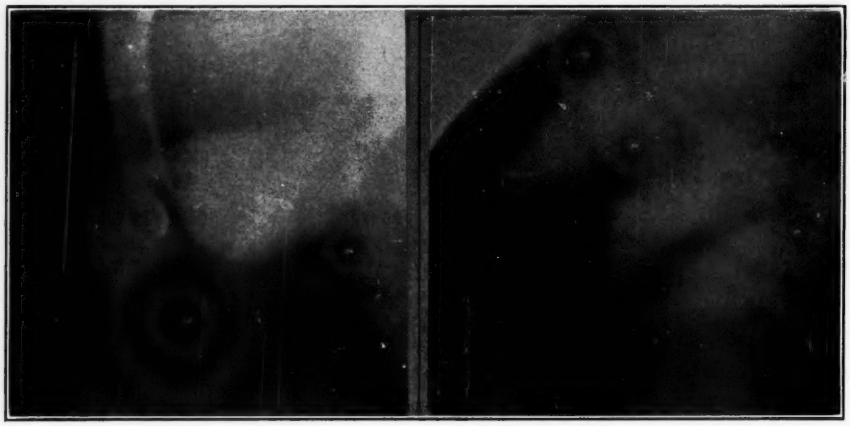
to the optimum time for the normal gall bladder to empty itself. Variations occur with age and sex, as can be seen from the following results of Boyden and Fuller[12] and Boyden and Grantham.[13] Before puberty, boys show more rapid emptying than girls. After puberty, females show more rapid emptying than males. In old age women evacuate 81 per cent of the contents in thirty minutes; men, 65 per cent. There is very little difference in emptying time between female children and adult women. Boys, however, show much more rapid evacuation than adult males. Because of such variation, roentgenologists would do well to pay less attention to complete emptying as an important point in diagnosis. It is important to determine, however, whether the gall-bladder shadow (1) diminishes in size, (2) remains unchanged in size, or (3) increases in size.

Failure of the gall bladder to diminish in size after the proper technique has been used may be due to a number of conditions; such as, mechanical kinking of the cystic duct, ball valve obstruction of the cystic duct, milk of calcium bile with or without a cystic duct stone, spasm of the sphincter of Oddi mechanism, anomalies, adhesions, and reflex phenomena from lesions outside the biliary tract. Increase in the size of the gall-bladder shadow occasionally may be seen. An explanation of this occurrence may be found in the work of Ravdin and others,[67] who found that in dogs water could flow out of or into the lumen of the gall bladder. Practically all of these conditions which interfere with the emptying of the gall bladder, or even increase its size, have been rather loosely grouped together under the term "dyskinesia of the gallbladder." Further investigation is necessary to evaluate the meaning of this disturbance in function. For the present we are inclined to classify gall bladders which may show good or faint visualization after dye, yet which do not show proper dynamics after the fatty meal, as "partially functioning."

ANOMALIES OF THE GALL BLADDER

Congenital absence of the gall bladder is rare. Bower[11] was able to find 59 cases in the literature up to 1928, when he added 1 of his own. Gross,[34] in a more recent review, found a total of 73 cases of absence of the gall bladder and 28 recorded cases of double gall bladder. He states that the accessory gall bladder may be contiguous with the normal organ, under the left lobe of the liver, within the liver parenchyma, or in the gastrohepatic omentum. Boyden[14] is of the opinion that accessory gall bladder occurs in about 1 of every 3,000 or 4,000 human beings. He classifies this anomaly as: (1) vesica divisa or bilateral gall bladder, and (2) vesica duplex, either Y-shaped with two cystic ducts merged into one, or ductula, with two complex cystic ducts opening separately into the common duct.

A diverticulum of the gall bladder may occur along the free surface of the organ or even on the hepatic surface, anywhere between the neck and the tip of the fundus.[34, 82] Probably the most common congenital anomaly which can be demonstrated roentgenographically is the folded fundus. This has been described by Boyden,[15] who found that 18 per cent of a group of 165 individuals exhibited marked kinking of the gall bladder either between the body and infundibulum or between the body and the fundus (Fig. 26). The former group, he believes, represents merely an accentuation or a minor variation from the normal, which may be due to extreme modeling of the fossa vesicae felleae. The second group, which has been termed "phrygian cap," is characterized by a fixed, folded fundus. This condition, in itself, may be of no clinical significance, but it is important because it may



A. *B.*

Fig. 26.—Types of folded fundus. *A*, Fold between the body and the infundibulum, *B*, "Phrygian cap."

be confused roentgenographically with double gall bladder or with diverticulum of the gall bladder.

Anomalies in position of the gall bladder sometimes may be demonstrated by cholecystography. Gross[34] states that a normally formed gall bladder may be found within the liver substance, under the left lobe, posteriorly under the right lobe, in the transverse fissure of the liver, or "floating" in the mesentery. The last named position may be important because of the tendency for twisting of the suspensory attachments, which might result in infarction and gangrene of the gall bladder. The intrahepatic gall bladder[48] is important because it may be completely missed at operation. This condition is impossible to diagnose preoperatively, except by cholecystography. The intrahepatic gall bladder is higher than normal and maintains its position in relation to the liver shadow. Its lower limit may be on a level with, or

above, the inferior edge of the liver. Often posteroanterior, oblique, and lateral roentgenographic exposures are necessary to demonstrate the true condition.

Our experience with the roentgen diagnosis of gall-bladder disease in children has been limited. In a series of 226 cases of gall-bladder disease in children under the age of 15 years, collected by Potter,[66] 140 had calculi; 59, cholecystitis; and 2, primary malignancy of the gall bladder. It is a well-known fact that the clinical symptoms of gall-bladder disease in children may resemble the symptoms of appendicitis and may be accompanied by it. There is also good evidence to indicate that peritoneal irritation interferes with the emptying of the gall bladder.[57] This may account, in part, for the relationship which has been mentioned. In the nonacute cases a cholecystogram, as well as an examination of the stomach and small intestines, may be of definite value in the diagnosis.

Sources of error associated with cholecystography by the oral method may be divided into (1) errors in technique and (2) errors in interpretation. The sodium tetraiodophenolphthalein should be kept in dark, air-tight bottles, so that oxidation does not occur. Instructions, written in detail, must be given to the patient. The roentgenograms must be of diagnostic quality and should be made with the shortest possible exposure time to prevent motion.

We insist upon visualization of dye in the bowel before rendering an opinion of an "abnormally functioning gall bladder." In this way we can be certain that the patient has ingested the dye and that vomiting or diarrhea has not interfered with its absorption from the gastrointestinal tract. Anzilotti[7] states that certain diseases outside the biliary tract which may produce nonvisualization of the gall bladder are pyloric and duodenal ulcers, pancreatitis, appendicitis, hyperthyroidism, diabetes, cancer, and some infections. Mann[47] has demonstrated pregnancy as a cause of nonvisualization. We have observed variable results in the test in patients with cardiac disease. Gibbon and Cooper[27] found that about 80 per cent of a group of 81 uncontrolled diabetics gave faint shadows or no visualization of the gall bladder by cholecystography. There is some evidence[64] to show that gall-bladder visualization and emptying may occur earlier in patients with uncontrolled diabetes. It may be necessary to arrange the technique accordingly in this group of individuals. Good and Kirklin[29] do not consider that extrabiliary conditions affect the function of the gall bladder. They studied 167 proved cases who showed abnormally functioning gall bladders associated with extrabiliary disease and the cholecystographic findings were accurate in 98.1 per cent.

Cholecystography is an accurate but not infallible means of detecting disease of the biliary tract. One can readily appreciate that it

is not a procedure to be used injudiciously, without proper regard for the many conditions which may affect the correct interpretation of results. If one may utilize the statistics of Kirklin[42] as an index, the general accuracy of this type of examination is about 90 to 95 per cent. This does not include cases studied after operations on the biliary tract. The value of cholecystography after cholecystostomy has not been definitely determined. This is indicated by the following table.

AUTHOR	NO. CASES REPORTED	PER CENT SHOWING FUNCTIONING GALL BLADDER
Spurling and Whitaker[80]	12	0
Fleming[26]	36	2.7
Saint[73]	18	38.9
Jenkinson and Foley[40]	28	68.0
Eliason and Ferguson[22]	28	21.4

Enough data are not yet available for us to determine the value of cholecystography in these patients, particularly in those individuals who may show clinical evidence of recurrence of gall-bladder symptoms, yet have a functioning gall bladder by cholecystography.

CHOLANGIOGRAPHY AND CHOLANGIOSCOPY

A small collection of barium in the second portion of the duodenum is sometimes noted during the course of roentgenologic examination of the gastrointestinal tract. This represents the ampulla of Vater and may be confused with a small diverticulum in this region. Retrograde visualization of the biliary tract during the course of a gastrointestinal examination is less common. Such may occur, however, if there is an obstruction in the duodenum distal to the ampulla which causes it to dilate or if there is, as a result of disease or operation, a fistula between the intestinal and biliary tract. Since 1927, methods have been devised for the direct visualization of the biliary tract following the injection of opaque media. The procedure is of value in demonstrating obstruction, in outlining stones, strictures, or fistulas, and in delineating dilatation of the biliary system. Occasionally the injection may help to flush out small stones or debris which are producing symptoms. Two methods are available: (1) immediate cholangiography, done at the time of operation; and (2) delayed cholangiography. The first method has been described by Robins and Hermanson.[71] When the abdomen is opened, the radio-opaque substance (hippuran) is injected through the common duct before the gall bladder is disturbed and films are exposed immediately. If the duct is patent, incision and exploration are unnecessary. If the films show evidence of obstruction, the common duct is opened and explored

for the cause of the obstruction. After this procedure is completed, a T-tube or catheter is inserted, hippuran again injected, and a second film exposed. The surgeon is then able to determine whether or not the obstruction has been removed.

Delayed cholangiography consists in the roentgen demonstration of opaque material injected through a catheter, tube, or biliary fistula at some time after operation, before the drainage tract is allowed to close. The procedure is quite simple. We have injected lipiodol, or equal parts of lipiodol and olive oil, under fluoroscopic guidance in many of these patients (Figs. 27 and 28). Films are exposed at intervals, depending upon the indications. The necessity for roentgenoscopic control cannot be overestimated, for it may prevent untoward reactions due to overdistention or may reveal stones or spasm which are not apparent in the roentgenogram. Hufford[38] has pointed out

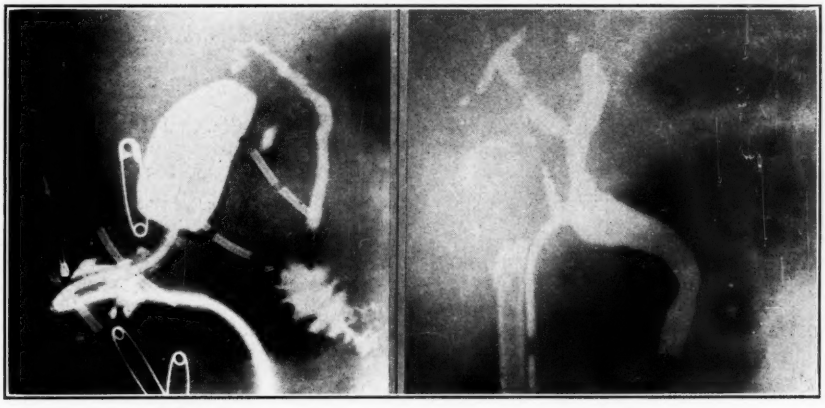


Fig. 27. Fig. 28.

Fig. 27.—Cholangiogram. We have considered this as a normal appearance. The cholecystostomy tube, gall bladder, cystic duct, common duct, and duodenum can be identified. Note that none of the opaque oil has passed up into the hepatic ducts.

Fig. 28.—Cholangiogram. The concave filling defect which obstructs the common duct is due to a nonopaque stone. Note the dilated common duct and hepatic ducts. The opaque oil outlines many of the smaller radicles which are widely dilated.

the value of the procedure as a complementary method in determining the proper time to allow closure of the operative wound. Hicken and others[36] also have showed the advantage of cholangiography. The procedure is practically harmless and may provide a great deal of assurance to the surgeon and to the patient soon after operations on the biliary tract.

SUMMARY

We have attempted to point out the value of roentgenographic diagnosis of surgical diseases of the biliary tract. Close cooperation between the surgeon and the radiologist will afford opportunity for early diagnosis, prompt treatment, and better results.

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THE ANATOMY OF GALL-BLADDER INCISIONS

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A SURGICAL incision for the exposure of the biliary passages should satisfy two requirements: adequate access to the structures sought, and absence of postoperative disability due to the incision itself. Unsightly scars are distressing to the patient and to the operator. Postoperative weakness of the abdominal wall may be due either to a partial paralysis of a rectus muscle or to a diastasis of the rectus muscles.

Vertical incisions through the substance of the rectus muscle do not seem to cause disability. This is apparently due to the scarring of the muscle to the rectus sheath which, in effect, creates an additional, diffuse, tendinous inscription. This statement is made from an experience with dissected rectus scars in the lower half of the abdomen. (In the last ten years, with a material consisting of about 1,800 cadavers, I do not recall a single scar of a gall bladder incision.) It would seem that any postoperative disability of the rectus muscle is due to an injury to its motor nerve supply. Experience with diastasis of the rectus muscles in the lower part of the abdomen gives no indication that the separation is the result of any anatomic peculiarity. Can it be that the postoperative diastasis in the upper part of the abdomen is due to the difficulty of securing sutures effectively in the loosely imbricated fibers of the sheath?

In order to present anatomic factors which may merit consideration in planning an incisional technique, the relations of the area will be summarized under the following headings:

I. The anatomy of the skin and subcutaneous tissue as related to incisions.
II. The composition of the rectus sheath.
III. The course of the nerves to the rectus muscle.

I. THE ANATOMY OF THE SKIN AND SUBCUTANEOUS TISSUE AS RELATED TO INCISIONS

In 1861 Langer, on the basis of earlier observations of Dupuytren, Malgaigne, and others, worked out the directions of the principal fiber patterns in the adult human skin by puncturing the skin with an awl. In general, a round awllike instrument thrust into the skin, by separating the principal fiber bundles, produces a slitlike opening. Upon withdrawing the awl every normal movement of the body tends to keep the slit edges in approximation. A skin incision made to coincide with the direction of the fibers also tends to close. An incision made at right

angles to the split-pattern gapes with every movement. I have shown that the subcutaneous tissues have the same cleavages as the true skin. Kocher correlated these skin cleavages with surgical incisions. Fig. 1, made from a new preparation, shows the skin cleavages in the upper part of the abdomen. Obviously, it would be difficult always to make the initial skin incision for exposure of the biliary passages to coincide completely with this pattern. Although an incision at right angles to the cleavages would result in a wound more adapted to maintain drainage,

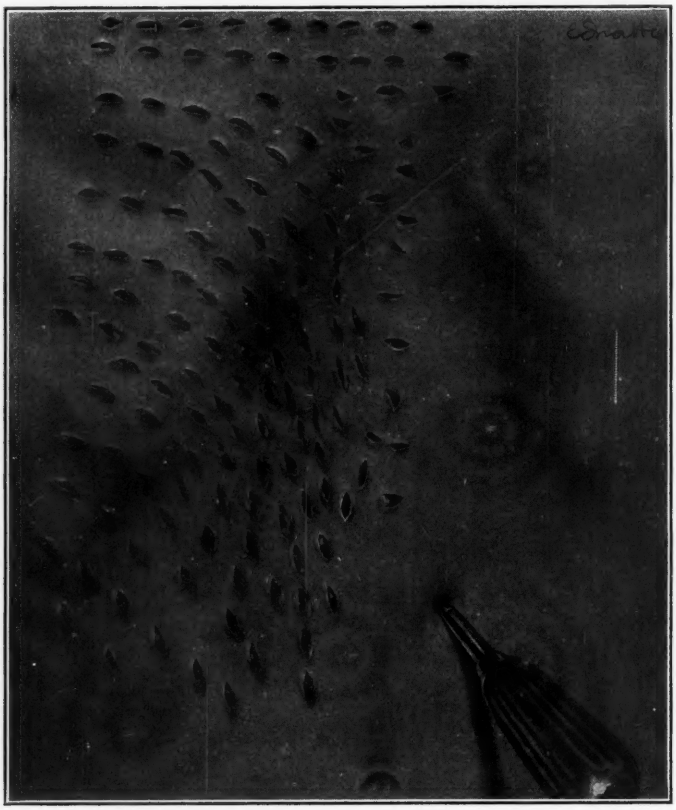

Fig. 1.—Splits in the skin produced with an awl. These splits indicate the principal fiber directions. Note that the superficial layer of cleavages is at right angles to the deep layer in a number of places, such as in the subcostal area.

in view of the end result, the drain should probably be brought through that part of the original incision, or through a stab incision which coincides with the direction of splitting.

It is neither necessary to remember the cleavage patterns nor to have a chart at hand. Thumb and finger will readily determine the directions of elasticity and rigidity of the skin. The splits run in the direction of the inelasticity and hence incisions are preferably made in this direction. This method permits the incision to be adapted somewhat to the variations in individual anatomy.

II. THE COMPOSITION OF THE RECTUS SHEATH

For our present purposes the rectus muscle in the upper part of the abdomen may be considered surrounded by two aponeurotic laminae derived from the internal oblique muscle. These reunite at the linea alba. In this manner a flat capsular aponeurotic sheath is formed. The muscle is firmly attached to this sheath at the several, irregularly transverse, tendinous inscriptions.

In the upper part of the abdomen there is always aponeurosis in front of, and behind, the rectus muscle. The superficial lamina of this sheath

Fig. 2.—Dissection to show the nerve supply and the sheath of the rectus muscle. The continuation of the fleshy fibers of the transversus abdominus muscle behind the aponeurotic sheath may be confusing in well-muscled individuals.

is joined and reinforced by the aponeurosis of the external oblique muscle. This layer remains muscular until it is well over the rectus. Similarly underlying the deep lamina of the sheath is the transversus abdominus muscle which likewise does not become aponeurotic in this region until well under the middle of the rectus muscle. As a result, flat muscle is found both in front of and behind the aponeurotic rectus sheath in the upper part of the abdomen at the outer margin of the rectus muscle. These flat muscle layers many times are thin and pass unnoticed. In muscular individuals these muscle layers may be very prom-

inent, especially the inner one, the transversus abdominus muscle. Judging from frequent questions, this relationship is sometimes not sufficiently emphasized (Fig. 2).

III. THE COURSE OF THE NERVES TO THE RECTUS MUSCLE

The essential facts of the innervation of the rectus muscle are briefly stated. The muscle receives motor branches from the lower five or six intercostal nerves. As with other muscles receiving multiple segmental innervation, anatomic studies and clinical experience show much overlapping in the terminal arborization of nerves from adjacent segments. Especially in the upper part of the rectus muscle, injury of one intercostal nerve is not accompanied by a disabling paralysis. In the gall bladder area there are encountered the seventh, eighth, ninth and tenth intercostal nerves. The arrangement of nerves found in an adult white male cadaver (Fig. 2) may be taken as typical. Variations of one segment up or down in numerical origin are encountered, but the general curving course remains the same.

This indicates then that an incision through the flat muscles may be made parallel to the curving costochondral margin with comparative safety to the nerve supply of the rectus muscle. It may be necessary to cut the ninth (or eighth) nerve but, as noted above, the injury of one segment does not disable the muscle.

Upon leaving the rib margins, the nerves, with their small accompanying vessels, course between the internal oblique muscle and the transverse abdominal muscle until they pierce the deep inner lamina of the rectus sheath to enter the posterior surface of the rectus muscle near its lateral edge. This relationship seems to make unwise incisions parallel to the lateral margin of the rectus muscle. Further, caution is indicated in media retraction of the rectus muscle. Lateral retraction of the rectus muscle through a vertical sheath incision will not disturb the nerve supply. If it is desired to make a transverse cut in the rectus muscle, the points of entrance of the nerves may be visualized and avoided.

The anatomic facts which might be considered in making these incisions appear to be sufficiently at variance with one another that it is not surprising that some surgeons disregard them altogether and strive only for a wide exposure. However, an incision just under the right costochondral border gives good exposure and is anatomically the most favorable. Occasionally, due to individual variations, this incision will be too low for the best results in skin closure. An extension of the incision transversely through the rectus muscle is compatible with the nerve distribution. No objections on anatomic grounds can be raised to linea alba incisons.

PREOPERATIVE AND POSTOPERATIVE TREATMENT IN CASES OF OBSTRUCTIVE JAUNDICE

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OBSTRUCTION of the common duct is all too frequently considered a local disease. In reality the local site of obstruction is but an initiating incident in the more important general reaction following cessation of the normal flow of bile. Correction of the consequences of common duct obstruction naturally lies in the relief of the obstruction. However, surgical procedures designed to overcome the obstruction must wait until the patient is properly prepared for operation. No longer is immediate operation considered necessary. The preparation of the patient for operation is of primary importance in the necessary readjustment of the patient to the altered physiology following the obstruction to the outflow of bile.

Following obstruction to the common duct, a train of events occurs which result in widespread changes in the individual.[1] When the flow of bile from the liver is stopped either partially or completely, the liver becomes altered morphologically and physiologically, and the digestive processes become embarrassed. While the latter variation from normal is of consequence, the results of suppression of biliary outflow become of paramount importance in relation to liver function. Shortly following obstruction of the common duct, the liver becomes damaged, and it is for this reason that the patient presents a problem requiring careful study and preparation before operation is considered. This fact was well brought out by a symposium on obstructive jaundice by leading German surgeons,[2] where varying viewpoints were expressed regarding types of operative procedures, of the rôle of infection, and methods of treatment, but the one accepted fact was that damage to the liver parenchyma was the most important result of the obstruction. The concept that disordered liver funcion is the underlying defect associated with common duct obstruction has been widely accepted within the past decade.

The methods for evaluating liver function have been recently discussed by Snell[3] and Newman.[4] It is noteworthy that none of these tests has been completely trustworthy in depicting the status of the activity of the liver parenchyma. Newman[4] has pointed out that, since there are many functions of the liver, no one of the tests may be depended upon to tell us the whole story of hepatic insufficiency. Many of the functions of the liver are also carried on elsewhere in the body or are influenced by other organs. The relation of the liver to sugar metabolism is well known; yet this important function is greatly influenced by pancreatic and adrenal activity.

The measure of the elaboration of bile salts should afford a good criterion for liver function, but as yet we have no method for determining bile salt formation in the liver of intact patients. So far as we know, bile salts are formed solely in the liver.[5] This is corroborated by the fact that fetal bile has little or no bile salts present, indicating that this important hepatic function appears after the liver becomes more active when the offspring assumes independence from the maternal metabolic processes. An additional corroborative fact is the early loss of bile salts from the bile after obstruction of the common duct and the rather tardy return after release of the obstruction.[6, 7, 8]

In a series of cases Ravdin, Johnston, Riegel, and Wright[7] studied the return of bile salts in the bile following release of a complete obstruction of the common duct, and the earliest date when traces of bile salts could be found was seven days.

The care of the jaundiced patient must at all times be directed toward conserving the function of the liver under adverse conditions. It is for this reason that morphine should be used sparingly in the control of pain in these cases. In addition to the effect of morphine on the storage and mobilization of glycogen, it must be remembered that this drug is a respiratory depressant. Goldschmidt, Ravdin, and Lucké[9] have recently shown the effects of relative anoxic conditions on the ability of the liver to withstand the assault of anesthetics.

Recently Butsch, McGowan, and Walters[10] have condemned the use of morphine in controlling the pain associated with obstruction of the common duct on the ground that morphine increases intraductal tension, and therefore should increase rather than decrease pain. For many years it has been common practice to give morphine in common duct obstruction with excellent results as regards the control of pain. Morphine has an analgesic action which is capable of controlling pain even though the tension within the duct may be increased. The chief fault with morphine lies in its effect on the liver and is not concerned with its effectiveness in the control of pain. Butsch, McGowan, and Walters suggest the use of the nitrite series for control of stone colic; these drugs have a much more rational basis than morphine but are, as a rule, more fleeting in their action.

Frequently the pain associated with common duct obstruction can be controlled by bed rest and restriction of intake by mouth of food and fluid. During this period the patient should receive adequate glucose and saline solution by vein. This method assures the introduction of needed fluids and glucose and is not associated with the difficulties associated with the subcutaneous method. The rectal administration of glucose has been shown by Ebeling,[11, 12] Scott and Zweighaft,[13] Pressman,[14] and McNealy and Willems[15] to be quite ineffective. After

the period of acute colic has passed, the patient should be given a high carbohydrate diet supplemented by slow intravenous infusion of 10 per cent glucose in distilled water. By this latter means it is possible to introduce 100 to 300 gm. of glucose daily in addition to the carbohydrate taken by mouth.

The value of high carbohydrate intake in cases of jaundice from common duct obstruction has been stressed recently by Ravdin, Riegel, and Morrison.[16, 17] It was Ravdin and his associates, who in 1930 pointed out the beneficial effects of glucose in obstructive jaundice and indicated that the beneficial effects were associated with a partial restoration of glycogen reserve. In 1915 Opie and Alford[18] and Graham[19] showed that animals subjected to chloroform were better able to withstand its toxic effect if a high carbohydrate diet was given previous to the administration of the drug and indicated that in those animals least effected, there was adequate glycogen stored within the liver, and in those most susceptible, there were marked fatty changes in the liver. The relationship between the amount of fat deposited in the liver and the susceptibility of liver cells to necrosis has been well shown, as have the merits of high carbohydrate intake in decreasing the fat within the liver cell.

Glucose has long been advocated in the preoperative preparation of jaundiced patients to prevent postoperative bleeding, but until Ravdin's report[17] in 1930 calcium was given in addition to the glucose and it was thought by many that the calcium was the responsible agent. Calcium has had quite a vogue in the preoperative preparation of the jaundiced patient. The basis for its introduction was a fallacious assumption that there was a deficiency in blood calcium in the jaundiced individual. Since calcium is necessary for clotting of blood, the concept that there was a deficiency of calcium in jaundice formed a rational basis for explaining the bleeding tendency and resulted in much clinical data regarding the value of calcium therapy. In the light of the knowledge of the effectiveness of glucose to protect the hepatic cell, it is unfortunate that it is difficult to determine whether, in addition to calcium, glucose was also given; therefore much of the older data in regard to calcium therapy is of no value. Suffice it to say that there is no lack of calcium in the blood of the jaundiced patient, nor is there, as Gunther and Greenberg[20] have so well shown, a lack of availability of the calcium present except in the presence of a low plasma protein. This latter contribution has clarified our concept concerning the bleeding tendency in jaundice decidedly since in association with the view that there was a decrease in blood calcium in jaundice, there have arisen many theories regarding the cause of the bleeding, based upon a combination of calcium with bile salts, bilirubin, or some other substance which prevented its activity. Calcium is still being advocated[21] in treatment of the jaundiced patient, but at least it has been stripped of the prestige of a scientific basis.

With regard to the value of glucose in jaundiced cases, the opposite is true. Not only has the value of high carbohydrate intake been indicated by clinical data, but experimental studies as well have stressed its merit.

Not only does the glucose afford protection for the liver, but it is of importance in reparative processes after liver damage, as has been recently reemphasized by Snell and Bollman.[22]

An additional safeguard against liver damage is the administration of whole blood. The effects of anoxic states on the reaction of the liver to damage have been demonstrated by Goldschmidt, Ravdin, and Lucké,[9] and Judd, Snell, and Hoerner.[23] The mechanism for the effectiveness of blood transfusions in liver damage is not well understood, nor is it demonstrable from studies on the blood in jaundiced patients that there is consistently a decrease in the oxygen-carrying capacity. The transfusion of blood in jaundiced patients is not to be reserved for patients who bleed postoperatively, but is valuable as a preventive measure. New blood with normal clotting mechanism introduced into the patient has a rational basis in the supply of the necessary elements for clotting, and it undoubtedly is an important factor in prevention of and restoration from hepatic damage.

One of the most difficult questions relative to the jaundiced patient concerns the determination of the time when the patient is properly prepared for operation. Clute and Swinton[24] suggest a preoperative regime for five to twelve days. Ewald[2] states that one should wait no longer than two to four weeks but that longer periods of waiting even up to a year may not be particularly damaging. It is quite difficult to see the value of any time limit for the preparation of the patient, as many variable factors other than time may be present to influence the amount and nature of damage to the liver. There has long been the hope that some means of measuring accurately the bleeding tendency would afford a reliable test for deciding the time of operation. This has not been the case. Likewise liver function tests theoretically offer this possibility, but actually none of the tests of liver function has proved of merit in the determination of the possibility of bleeding in the jaundiced patient. This is probably due to the fact that the present methods are not definitive enough since they test only one or another phase of liver activity. Even when several tests are used routinely, the results are disappointing.

In 1930 Linton[25] reported that the sedimentation rate of the blood was useful in determining whether or not patients would bleed postoperatively. However, subsequent experience[26, 27] has not shown this to be the case. The sedimentation rate may be affected by many factors associated with jaundice, and it is hardly to be expected that this test would be distinctly prognostic.

Following occlusion of the common duct, the bilirubin level of the blood, as measured by the van den Bergh test, increases. This increase continues with an associated increase in generalized icterus for a variable period of time when, despite the fact that there is complete obstruction to outflow of bile from the liver, the serum bilirubin level reaches a plateau. When this plateau has been maintained for several days, we feel that the patient has become stabilized under the new environment and is best able to stand operation. We do not operate on patients with rising or falling levels of serum bilirubin. The mechanism for the stabilization of the level of serum bilirubin is not understood, but it is our experience that the patient withstands operation better and has less tendency to bleed after stabilization has occurred.

In the preparation of the patient for operation there are two objectives: (1) that the patient's general physcial condition be made as good as possible, and (2) that the hepatic parenchyma be restored to as nearly normal as conditions permit. The complication most feared is bleeding either before or after operation, and this complication is better prevented.

Following operation, similar conditions as obtained before operation are present and are treated in much the same manner. The release of obstruction to the outflow of bile does not immediately correct the effects of the obstruction. Bleeding which is not common before operation is to be feared because of the added source of hemorrhage, the fresh wound. Even when all visible bleeding points have been carefully tied at operation, there is a certain amount of oozing. The clot which forms is grossly abnormal in that it does not retract well. Much of the fresh postoperative bleeding is due to bleeding behind a clot, a mechanism which is well known to cause continued bleeding even in normal wounds. In many instances were it possible completely to clean out the old semiformed clot and allow for drainage of the blood, bleeding could be more easily controlled. Packing over the clot is a maneuver of little value, as it is in wounds in individuals with normal clotting mechanisms.

The causes ascribed for the bleeding tendency associated with jaundice consist not only of deficiency of any one of the elements concerned with clotting, but the presence of substances which are known to prevent clotting. The question of the relationship of calcium to bleeding in jaundice has been discussed above. Fibrin insufficiency has been suggested chiefly on the basis that the liver is a rich source of this material. Melchior[28] noted a marked decrease in blood fibrinogen and thrombin after hepatectomy in dogs. Moss[29] and Ravdin, Riegel and Morrison[16] have shown that there is not a deficiency in fibrinogen in jaundice. Barlik[30] was impressed with the liver as a storehouse and regulator of the antiprothrombin content of the blood and concluded that with liver damage this mechanism is lost. Bile salt increases in the blood have been surmised to occur in obstructive jaundice, and their presence was

assumed to interfere with clotting, either by direct action or by combining with elements necessary for clotting. Petren[31, 32] was able to increase coagulation time in vitro by the introduction of bile salts, but it was necessary to increase the bile salts to 0.2 per cent, a value much higher than has been found in the blood by many authors. Methods for analysis of bile salts in blood are not dependable, and a high bile salt level is not likely to be maintained. Bollman and Mann[5] found that bile salts are rapidly excreted if injected into the blood stream. Carr and Foote[27] present an unusual theory for the hemorrhagic tendency in jaundice. These authors assume that cysteine and mercaptans are increased in the blood in jaundice and that these substances are responsible for inhibiting clot formation.

The causes of the bleeding tendency have not been determined. All of the elements necessary for clotting have been suspected as being deficient, but collected data have not substantiated these assumptions. In addition, the presence of substances which might prevent clotting has not been proved. The knowledge of methods of preventing and treating bleeding in jaundiced patients has progressed farther than has the knowledge of the causes underlying the bleeding tendency in jaundice.

Postoperative bleeding in the jaundiced patient is best treated by attention to the wound, by frequent blood transfusions, and by the introduction of glucose solutions by vein. When bleeding continues despite these measures, it is worthwhile to remove the drainage tube from the common duct to prevent irritation from the tube.

Fluid intake should be controlled by supplying adequate fluids and salt to overcompensate for that lost not only through the usual channels, but also from the drainage of bile. For this reason, it is necessary to estimate total fluid loss. Continued loss of bile will cause the patient to lose not only large quantities of bile which are so necessary to digestion and assimilation of food, but also the constituents of bile, which loss constitutes a drain on mineral stores. This may be compensated for by returning the bile drainage to the intestine by use of the Jutte or Levine tube. This method of returning bile to the patient is usually troublesome, not only to the patient, but to the doctor as well. Even if carefully collected over twelve-hour periods, the bile has a tendency to spoil and is unpleasant to administer. To overcome this objection we have prepared lyophilized bile which can be given in tablet or capsule form. Lyophilized bile is quite different from ordinary tablets of fels bovis in that it will dissolve in water to form a substance resembling the original sample of bile from which it was prepared, not only in composition but in consistency, odor, and color. The material is prepared after the method of Flosdorf and Mudd[33]* and forms from the bile light

*We have found a process for making dried bile preparations which is less complicated. This will be reported in a subsequent paper.

fluffy yellow crystals which can be preserved indefinitely. This material may be prepared from clean fresh human drainage bile or from fresh ox bile. We feel that lyophilized ox gall bladder bile is better than human drainage bile because of the presence of bile salts in high concentration.

The management of the T-tube drain persents several interesting and important considerations. Frequently during the first few days the material draining from the T-tube will appear bloody. It has been suggested that the cause for this is the sudden decompression of bile ducts.[34, 35] Slow decompression such as is commonly practiced in relation to the urinary tract in retention has been suggested. This is practically impossible to accomplish since the common duct must be opened for the introduction of the T-tube and the loss of even a few cubic

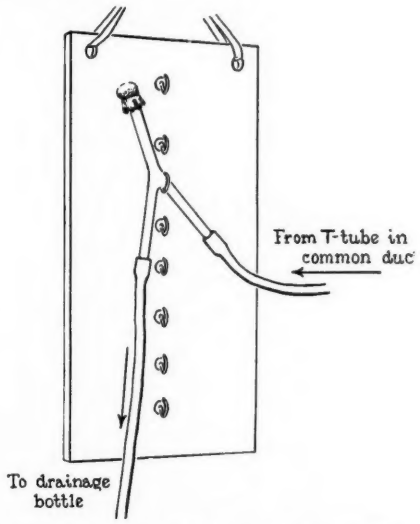

Fig. 1.—Simple method for gradual decompression of the common bile duct.

centimeters of bile from the ductal system will reduce the pressure markedly. What is probably more true is that following drainage of the common duct, the intraductal pressure is suddenly decreased from a value of about 300 mm. of water not only to zero, but even lower, because actual suction is applied by the habit of allowing the tube to drain into a bottle on the floor. By this means there is exerted by the drag of the column of bile a suction on the common duct of several feet of water. This can be overcome by several methods. The simplest is the use of a small bottle lying next to the patient at the level of the abdominal wall as suggested by Reid[34] or the use of a tube extending into the bottle, large enough to break the bile column. Methods more easily controlled which produce a reasonable intraductal pressure and allow the bile to be collected in a receptacle on the floor are prepared by placing an impediment to the outflow of bile. This can be accomplished by one of

two simple methods. The first is one commonly used in decompressing the urinary bladder. One arm of a glass Y-tube is connected to the T-tube in the common duct; another arm is connected to the collecting receptacle. The third arm is covered with sterile gauze to prevent contamination, but otherwise is left open to provide a vent for breaking the column of bile. The glass Y is then attached to a board, the height of which may be adjusted to any desired pressure level (Fig. 1).

This apparatus is quite effective and easily prepared and controlled. A somewhat more elaborate apparatus for controlling intraductal pressure and which has a pressure-recording device attached may be made by the use of a glass pressure box through which courses a loose thin rubber tube. Air forced into the pressure box compresses the tubing and prevents the exit of bile until the pressure in the duct reaches a pressure higher than that exerted within the pressure box (Fig. 2).

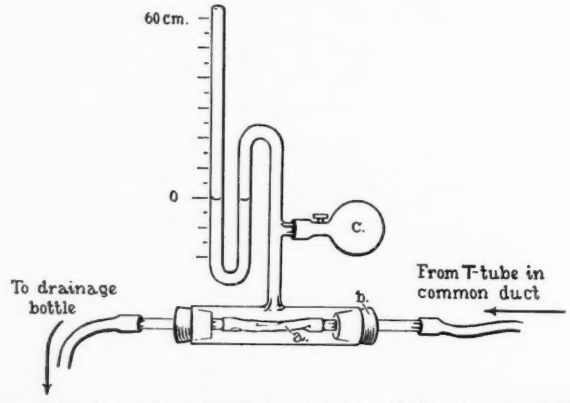

Fig. 2.—Author's method for decompression of the common bile duct.

Removal of the T-tube from the common duct should be accomplished as early as possible to prevent excessive loss of bile and ascending infection into the bile ducts. It is wise before the tube is removed to inject iodized oil under fluoroscopic control to determine whether the duct is patent to the duodenum. Even though the common duct is carefully explored at operation, it is possible for stones to be overlooked and visualization of the duct with a radiopaque substance is of value. If stones are present, they may be dissolved by the injection of ether as suggested by Pribram.[36] The tube should not be removed until it is ascertained that there is free passage of bile into the common duct.

In addition to the prevention of suction on the common duct, these methods maintain a steady gentle pressure within the common duct, tend to force bile into the duodenum, and minimize the amount of bile lost through the drainage tube.

In the management of cases of obstructive jaundice, the care before and after operation is of importance not only in the prevention of postoperative deaths, but also in the early restoration to health to these

patients. The problem of the jaundiced patient is not a simple problem concerned with the release of mechanical obstruction to the outflow of bile. The patient with obstructive jaundice is ill from the effect of changes incident to the obstruction and suffers from an illness which is widespread in its effect. The attack on the local problem must wait until the patient is properly prepared and attempts are to be made to simulate normal physiologic conditions as closely as is possible throughout the entire course of treatment.

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PERSONAL EXPERIENCES IN THE TREATMENT OF BENIGN OBSTRUCTING LESIONS OF THE BILIARY TRACT

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AS a participant in the symposium on the liver and gall bladder I have been asked to discuss obstruction of the common bile duct exclusive of malignancy. In view of the desire of the editors of SURGERY that the papers shall cover only essential details, I shall discuss briefly the following: (1) the causes of obstruction of the common duct; (2) some of the factors which might lead to failure to recognize the condition when it is unassociated with jaundice; (3) the recent investigations by Butsch, McGowan, and me[3, 4, 9] of biliary pressure associated with biliary colic; and (4) the recent studies of McGowan and Knepper on duodenal motility and its effect on the common bile duct. The investigations and studies mentioned are of clinical significance to that group of patients who continue to have biliary colic subsequent to cholecystectomy and exploratory choledochostomy.

Benign obstructions of the common bile duct are the result of (1) calculi formed, for the most part, in the gall bladder and extruded through the cystic duct into the common duct; (2) inflammatory lesions of the pancreas and of the wall of the common bile duct and of the intrahepatic ducts; (3) inflammatory tumors of the head of the pancreas with and without duodenal ulceration; (4) strictures of the common bile duct, usually traumatic in origin; (5) benign tumors of the common bile duct such as neurofibromas; and (6) functional spasm or inflammation of the sphincter of Oddi or of the duodenal portion of the common bile duct.

STONES OF THE COMMON BILE DUCT

The most common cause of obstruction of the common bile duct is biliary calculus. These stones, for the most part, are formed in the gall bladder and enter the common duct through the cystic duct. Such stones are usually faceted, although occasionally they may be ovoid. In some instances primary stones will form in the common bile duct. These are usually soft and are composed, for the most part, of bile pigment. Whereas it is usually thought that the presence of stone in the common bile duct manifests itself by typical attacks of biliary colic associated with jaundice, such is not always the case, for frequently stones in the common duct may produce biliary colic without jaundice or a feeling of discomfort subsequent to eating and without the nausea that results from pylorospasm. The possible presence

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of unsuspected stones in the common bile duct always should be remembered in operating on the gall bladder. Most stones of the common duct can be palpated with the thumb and forefinger. However, some stones, when single and small and when in the ampulla, cannot be palpated. In these cases and in all other cases of stone of the common duct, however, the presence of the stones is indicated by enlargement of the duct or by change in its color. When the common duct is opened and explored and stones have been removed, exploring scoops of increasing size should be passed gently through the sphincter of Oddi into the duodenum. This will permit overlooked, small, hepatic stones to pass the sphincter into the duodenum. I think it is well to emphasize again that, if patients have or have not undergone previous operations on the biliary tract, the absence of jaundice does not exclude the possibility of stone in the common bile duct. In addition, stones in the common bile duct may manifest themselves clinically only by producing intermittent fever, and sometimes this fever is not associated with attacks of abdominal pain.

OBSTRUCTION OF THE BILIARY TRACT AS THE RESULT OF INFLAMMATORY LESIONS IN THE HEAD OF THE PANCREAS

In approximately 10 per cent of a group of 500 patients on whom I have operated for benign, obstructing lesions of the common bile duct, I have failed to find stones in the common bile duct when it was opened and the interior carefully explored. In these cases there has been an inflammation of the pancreas, cholangeitis, and the bile frequently has been turbid. Culture of the bile has revealed, in most instances, a Gram-negative bacillus, either in association with, or not in association with, streptococci and staphylococci. In most of these cases the gall bladder is inflamed and infection can be demonstrated to have extended from the gall bladder, through the wall of the common bile duct and probably through the adjacent lymphatics to both pancreas and liver. In these cases removal of the gall bladder and prolonged drainage of the common bile duct have sufficed, in practically all cases, completely to eradicate the attacks of pain and jaundice. Many of these patients have been followed for a period of five years subsequent to operation.

There is a group of deeply jaundiced patients, in exploration of whose abdomens a tumor is found in the head of the pancreas. The tumor usually is thought to be malignant, and usually it is; but some of these patients, subsequent to cholecystenterostomy performed for relief of the biliary obstruction, have remained well for periods longer than five years. In a group of 113 patients[22] on whom cholecystenterostomy was performed at the Mayo Clinic for tumors of the head of the pancreas, 15 per cent were living and well five years after operation. This leads to the assumption that the lesion in the head

of the pancreas in this 15 per cent was not malignant but inflammatory. In such cases, although a section removed from the head of the pancreas would clarify the diagnosis, the risk of such a diagnostic procedure has not been thought to be warranted in the light of the fact that the surgical treatment employed is practically identical, whether the tumor is inflammatory or malignant. That this percentage of patients, who were afflicted as has been described, lived longer than five years after operation, not only makes the outlook for such patients more hopeful but affords an argument in favor of surgical procedures for them.

On several occasions I have operated on patients who had ulcers in the posterior wall of the duodenum, with perforation into the pancreas. Symptoms were identical with those of disease of the biliary tract. The intermittent pains and obstruction of the common duct in these cases were attributable to the perforation of the ulcer into the pancreas and the associated edema of the pancreas, which produced stasis in the pancreatic portion of the common bile duct. In these cases a previous history of a type of dyspepsia characteristic of ulcer assisted in the differential diagnosis, and gastroenterostomy usually has resulted in healing of the ulcer and relief of symptoms. It should be a routine, therefore, in the course of all operations on the biliary tract, particularly when there is a question of intermittent obstruction of the biliary tract, to palpate both the posterior and anterior walls of the duodenum. This examination should be made even though roentgenologic examination of the duodenum may have given a negative result, for occasionally ulcers are situated so low in the posterior wall of the duodenum that they may be overlooked in the roentgenologic examination.

STRICTURES OF THE COMMON BILE DUCT

Strictures of the common bile duct usually are traumatic in origin and manifest their presence by a history of prolonged biliary drainage subsequent to operation on the gall bladder or by the appearance of jaundice soon after such a procedure. In an occasional case obliterative cholangeitis may be the cause of the stricture of the common duct.

The treatment of stricture of the common bile duct, and also of external biliary fistula associated with stricture of the common bile duct, always is surgical. Although various procedures have been described, the most effective and lasting in their beneficial results have been choledochoduodenostomy or hepaticoduodenostomy. This is an anastomosis between the stump of the duct above the stricture or above the fistula and an opening in the duodenum. An accurate anastomosis is made between the edges of the duct and an opening made in the duodenum, thus obtaining a mucous membrane union. It is not always

possible, however, to employ this procedure. In order to do so, it is necessary that sufficient duct be present above the stricture and that the duodenum be susceptible of sufficient mobilization to allow accurate anastomosis. When this is not the case and the stricture is found to involve practically the entire length of the duct, the surgeon has to be content either with establishment of an external biliary fistula, to be coned out and transplanted into the stomach or duodenum at a later time, or with insertion of a catheter or T-tube, one end of which is in the intrahepatic duct and the other in the duodenum, bridging the gap between with adjacent tissue, occasionally with omentum. Removal or passage of such tubes is almost always followed by recurrence of the stricture. Such an undesirable outcome is avoided when accurate choledochoduodenostomy or hepaticoduodenostomy has been made. In a few cases of small, localized stricture of the common bile duct, not completely obstructive, excision of the strictured portion, with anastomosis of the normal ends of the duct, has been followed by good results. When, however, scar tissue is allowed to remain, even though the lumen of the duct has been increased by application of the Heineke-Mikulicz principle, the scar tissue previously formed, associated with that which follows the plastic procedure, again may produce obstruction of the duct.

In a group of 29 cases in which resection of the common or hepatic bile duct or the ampulla of Vater was performed and which I reported before the meeting of the Southern Surgical Association in 1931,[19] recent follow-up studies have been made; 48.3 per cent of the patients were living and well more than five years after operation. To date, my series of strictures of the common bile duct numbers 51 cases with a hospital mortality for the entire group of 13.7 per cent.[12, 13, 21] Most of these patients were deeply jaundiced at the time of operation. The result in all operations for stricture, providing accurate anastomosis can be made between the stump of the duct and the duodenum, is dependent on the degree of infection of the wall of the duct itself as well as that of the liver, for, if an unusual amount of inflammation exists in either of these structures, the obstruction may recur.

BENIGN TUMORS OF THE COMMON BILE DUCT

Benign tumors of the common bile duct are exceedingly rare; most tumors involving the extrahepatic biliary ducts are malignant.

In 1930 I operated upon a patient who had a localized neurofibroma, 1 cm. in length and 1 cm. in width, at the junction of the common and hepatic ducts.[5] The neurofibroma was excised and the two ends of the hepatic duct were anastomosed with the end of the common bile duct. Although the patient had some evidence of a mild degree of obstruction of the common duct during the first year and in the

years following, she was without evidence of disease of the biliary tract in 1935 when Comfort and I[6] reexamined her.

SPASM OF THE SPHINCTER OF ODDI AND OF THE DUODENUM

The introduction of choledochography, or visualization of the common and hepatic ducts after introduction of an opaque substance, such as brominol or lipiodol, has assisted materially in studying the pathologic physiology of the common bile duct. Not only do choledochograms afford an indication of the size of the duct but they also reveal the presence of persisting filling defects attributable to stone; of persisting obstruction the result of pancreatitis, both with and without reflux of the media up into the duct of Wirsung; of persisting inflammation of the lower end of the common bile duct; or of sphincteritis or spasm of the sphincter of Oddi. Although it is recognized that persisting stones in the common duct will cause persistence of symptoms of disease of the biliary tract, it is not generally recognized that pancreatitis may continue to do the same thing. Visualization of the common bile duct by choledochography has shown, however, that persisting pancreatitis will cause, in the common bile duct, continued stasis which may be responsible for recurrence of pain as well as possible recurring formation of stone in some cases.

The problem of abnormal function of the sphincter of Oddi has been called to attention by Mirizzi, by McGowan, Butsch and Walters, by Walters and Thiessen, and by Pavel.[15, 16] The last named author described cases of spasm of the sphincter of Oddi producing jaundice. Butsch and McGowan, of the Mayo Foundation, combining studies of choledochography with studies of pressure within the common bile duct, found that the pressure within the common ducts of patients who had biliary colic attributable to spasm of the sphincter of Oddi, increased to as much as 200 or 300 mm. of water.[3] Using a substance opaque to the Roentgen rays to measure the intraductal pressure in these cases and examining the duct under the fluoroscope, they demonstrated that in the presence of spasm of the sphincter of Oddi many of the smaller intrahepatic ducts filled. With the administration of amyl nitrite or nitroglycerin, spasm of the sphincter of Oddi subsided, pain ceased, intraductal pressure dropped to within normal limits, and the opaque substance left the hepatic and common ducts. To determine whether this effect was confined to the sphincter of Oddi alone, or whether it might involve the duodenal portion of the common bile duct, studies of intraduodenal pressure were carried out by McGowan and Knepper, of the Mayo Foundation. These investigators injected barium into the duodenum through a duodenal tube orally inserted and injected brominol into the common bile duct. On examining these structures by fluoroscopy, the investigators were able to show that in

some cases morphine produced spasm of the second portion of the duodenum and that it produced, also, what appeared to be spasm of the sphincter of Oddi, with increase in the pressure within the common duct. When amyl nitrite or nitroglycerin was administered, the spasm of the duodenum subsided, the lower end of the common bile duct relaxed, the brominol left the intrahepatic and common ducts and entered the duodenum, and relief of pain was obtained.

In some cases in which biliary colic continued subsequent to operation on the gall bladder, these conditions of spasm were found to occur both in the presence of, and in the absence of, stones in the common duct. It should be emphasized that stones in the common duct are usually the cause of such recurring colic and always should be regarded as the probable cause of the pain until the duct has been opened and thoroughly explored for stones. When stone is not found, however, the possibility that the spasm of the sphincter of Oddi or of the duodenum is a causative factor must be borne in mind. If the former, dilatation of the sphincter of Oddi frequently will give relief of the pain; whereas, if the pain is attributable to increased duodenal pressure from spasm, reduction in intraduodenal pressure can be accomplished by duodenojejunostomy as Gray has demonstrated. This has been tried and, although too short a time has elapsed to be certain of the end results, relief of the increased duodenal pressure and relief of pain have been demonstrated.

JAUNDICE, A COMPLICATING FACTOR IN OBSTRUCTION OF THE BILIARY SYSTEM

Jaundice complicating obstructing lesions of the common bile duct introduces the tendency to excessive bleeding following surgical procedures. Jaundiced patients need scarcely ever be considered as candidates for immediate or emergency surgical procedures. This is particularly true when it appears that the jaundice has been fluctuating in intensity. A period of delay allows study of the function of the kidneys, the liver, and the other parenchymatous organs and makes it possible to know the progress of the jaundice and particularly whether it is subsiding. Operation should be delayed until maximal reduction in jaundice has occurred. Studies of the coagulation time of the blood in such cases afford valuable indices not only of the tendency to bleed but also of the function of the liver. In my experience, a prolonged coagulation time, when a patient has been jaundiced, usually has indicated more damage to the parenchyma of the liver than can be considered an average amount for jaundiced patients.

Whereas the method of studying coagulation of the blood described by Lee and White afforded valuable gross evidence of wide variations in coagulability of the blood, the introduction by Nygaard and Baldes[1, 12] of a physicoelectric method in which, by means of a photoelectric cell

and an electric recording apparatus, an exact curve of the rate of blood coagulation can be recorded has been of great value. By giving an indication of disturbed coagulability prior to, as well as subsequent to, operation, this apparatus has given the first indication of approaching hemorrhage.

By far the greatest aids to hastening the coagulability of the blood of jaundiced patients have been solutions of glucose and of calcium chloride given intravenously and blood transfusion. Glucose and calcium chloride, intravenously injected, have been used as a routine, in preparation of jaundiced patients, at the Mayo Clinic since 1921.[18] These injections have been supplemented by blood transfusion given the day prior to operation if the patient has been deeply jaundiced or if the jaundice has been present for more than an average time. When the jaundiced patient is operated upon, surgical treatment should be directed toward relief of biliary obstruction with as little disturbance of tissue as possible. To this end I have frequently resorted to cholecystostomy rather than to cholecystectomy, since removal of the obstructing lesion in the common bile duct is the point to which surgical attention of necessity is directed. At the same time, of course, stones in the gall bladder should be completely removed to prevent their entering the common bile duct at a later time, causing the biliary obstruction to recur. From my having operated upon approximately 500 such patients in the last twelve years, I have become convinced that for deeply jaundiced patients the decreased risk of cholecystostomy, as a part of the removal of a stone from the common duct, far overshadows the fact that in a few of these cases it will be necessary to perform cholecystectomy at a later time.

CHOLEDOCHOGRAPHY

Following the recommendations of Overholt, Mirizzi, Bartlett, and others, choledochography has been a postoperative routine on my service at the Mayo Clinic since 1934. I do not remove a T-tube inserted in the common bile duct at the time of operation until postoperative choledochograms have revealed that the previously dilated duct has returned, subsequent to operation, to normal size and that there are no visual filling defects apparently attributable to stones retained in the duct. The advantages of such methods of study of the common bile duct have been stressed in previous communications.[20, 23]

CASE REPORT

In a recent case the patient was an obese man, 50 years of age, on whom cholecystectomy had been performed elsewhere and from whose common bile duct one stone had been removed at the clinic. Postoperative choledochograms revealed a circumscribed, negative shadow in the lower portion of the common bile duct, as though a stone were present. When the T-tube was closed, symptoms resembling

those of biliary colic occurred. A few cubic centimeters of ether were introduced into the common duct through the T-tube, as suggested by Pribram, at first undiluted and then mixed with an ethyl alcohol oily substance. This produced visual fragmentation of the shadow of what had seemed to be a single stone. Consequently amyl nitrite was administered in the course of an attack of pain and apparently relaxation of the lower end of the common duct occurred, allowing the fragmented particles of stone to be expelled spontaneously into the duodenum. Subsequent choledochograms gave evidence of a normal looking common bile duct. Closure of the T-tube for more than ten days was not followed by any discomfort and since the T-tube has been removed the patient has not had abdominal discomfort. On other occasions, even as long as three months subsequent to choledochostomy, persisting pancreatic obstruction has been noted and has subsided after more prolonged drainage.

SUMMARY

The condition which most frequently produces obstruction of the common duct is biliary calculus. Less frequent causes of obstruction are inflammatory lesions of the pancreas, associated with cholangeitis and strictures of the common bile duct. Jaundice, as well as chills and fever, may be absent. Stones in the common bile duct manifest their presence by enlargement of the duct or changes in its color and, if the common bile duct is enlarged, it should be opened and searched for stones with exploring scoops. In an occasional case of stone in the common duct the only symptom will be pylorospasm or intermittent fever.

Inflammatory tumors of the head of the pancreas may simulate carcinomatous tumors. Such enlargements may occur primarily, or secondary to infection in the gall bladder, or secondary to perforating ulcers of the posterior wall of the duodenum.

Strictures of the common bile duct are usually traumatic in origin and are best treated by choledochoduodenostomy or hepaticoduodenostomy if sufficient duct remains above the stricture to allow its anastomosis with the duodenum by means of an opening in the latter structure.

Recent studies by McGowan, Butsch, and Knepper on the effect of spasm of the duodenal portion of the common bile duct or of the sphincter of Oddi have shown that such spasm, occurring in human beings, can cause a type of pain similar to that of biliary colic, with increased pressure in the common bile duct and in the duodenum. With administration of amyl nitrite or nitroglycerin the spasm disappears, accompanied by relief of pain and a drop in pressure within the duodenum and within the common duct. These manifestations may be the accompaniment of stone in the common bile duct and the fact that a stone is not present can be determined only by intraductal exploration.

The presence of jaundice in a case of biliary obstruction requires particular attention to control the tendency to bleeding. Solutions of glucose and calcium chloride, given intravenously, and transfusion of blood form the most effective medical methods of combating this tendency. These methods should be applied preliminary to, and following, surgical relief of the biliary obstruction.

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LIGATION AND REFRIGERATION OF INTESTINE

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IT HAS been shown elsewhere[1] that the limbs of animals can withstand at least 15 hours of deprivation of blood at room temperature and periods of up to 54 hours at ice temperature. On the other hand, slight elevations of temperature greatly shorten the period of endurance. The literature dealing with both the tolerance of local asphyxia and the constitutional effects (shock) has been considered in other papers.[2]

Valid comparisons between the resistance of the peripheral tissues and of the viscera, therefore, can only be made at identical temperatures. This point, which is purely theoretical, was not tested experimentally. It was established, however, that the abdominal viscera differ rather widely among themselves in resistance to asphyxia, and from the data it appears possible that some of them, at least, are as resistant as the limb tissues at the same temperature.

Although the intestine is one of the more resistant of the abdominal viscera, surgeons seem to agree that it cannot survive more than six hours of complete lack of blood. In considerably less time than this it suffers damage which is expressed in dark discoloration, atony, and subsequent severe inflammation. An exact time limit under practical clinical conditions will probably be hard to establish, because infection, intoxication, and particularly fever must greatly reduce the period of resistance as compared with the normal bowel. This survival period is not exceeded in any warm-blooded species of animals and in some of them the limit is much shorter, perhaps because of higher body temperature or more active metabolism. Thus, the rat intestine seems to slough after 2 to 3 hours without circulation and that of the rabbit, after about 4 hours.

On the other hand, physiologists commonly keep various organs or tissues at refrigerator temperatures for periods of days, with retention of even the finer functions. As early as 1913, Cannon and Burket[3] pointed out that, when a piece of small intestine is kept on ice for 24 hours and then placed in warm saline solution, the occurrence of rhythmic contractions demonstrates preservation of the myenteric plexus. Their description of similar preservation for 6 or 7 hours when the vessels were merely ligated leaves it uncertain whether the bowel was exposed to body or room temperature.

As far as known, the present experiments are the first dealing with refrigeration of intestine in situ and subsequent restoration of circula-

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TABLE I

LIGATION AND REFRIGERATION OF INTESTINE

ANIMAL	PART LIGATED	DURATION HOURS	TEMPERATURE IN SALINE, C.	RECTAL TEMPERATURE, C.	LOCAL RESULT	SYSTEMIC RESULT
Rabbit A	10 cm. of empty small intestine	7	2°	33-31°	Pink color, firm tone of loop	Uneventful recovery; no important changes in blood count
Rabbit B	10 cm. of cecum and colon full of feces	7	6°	33-31°	No discoloration or atony	Death in 8½ hours, with fever 39° C., red cells slightly increased, leucocytes reduced
Cat A	12 cm. of empty small intestine	8	0-2°	32-31°	Pink color, firm tone of loop; no obstipation, diarrhea or distention	Cat unwell; subnormal temperature; red cell count fell from 9.1 to 5.7 millions in 15 hours; leucocytes rose briefly to 24,200; normal after 3 days
Cat B	10 cm. of empty small intestine	16	2-5°	31°	Same	Weakness, anorexia; no vomiting or fever; blood changes similar to above; normal after 5 days
Cat C	Lower half of small intestine, not all empty	4	2-8°	31-32°	Same	Temporary leucocytosis; gradual fall of red cells from 9.9 to 6.2 millions in 2 days; anorexia, constipation, marked prostration; recovery in 5 days
Cat D	Entire available intestine	3	2°	33°	Same	Brief leucocytosis above 100,000 cells; progressive fall of counts to 11,700 leucocytes, 2,700,000 red cells on sixth day; subnormal temperature, anorexia, trivial diarrhea; increasing prostration to death on seventh day

tion. The results conform to the physiologic experience with isolated organs and with my observations on refrigeration of limbs. The reduced temperature necessarily favors tissue preservation by inhibiting local metabolism (oxygen consumption and accumulation of waste products). For the same reason, instead of causing shock, it practically abolishes shock effects.

Tests of this kind can be performed by selecting a loop of intestine, protecting each limb of the loop at its base together with the adjacent mesentery with thin gauze or muslin, and applying a rubber ligature around the cloth, tightly enough to stop circulation but with avoidance of extra tension which would unnecessarily injure tissue or vessels. The loop is then dropped back into the peritoneum and the laparotomy wound closed with temporary sutures until the end of the test period. For tests with refrigeration, the loop is kept outside the abdomen by sewing the edge of the cloth to the margins of the wound, and the abdominal wall is closed around it so as to expose the loop up to a trifle above the ligature. The animal is then secured in a holder having a suitable slot in the bottom, so that the loop can be submerged in iced saline solution up to the abdominal wall, without wetting more than a very small surrounding area. The jar containing the saline solution is set in another vessel containing a mixture of ice and salt, and a thermometer is used to stir the saline solution frequently so as to make sure that the temperature in the immediate vicinity of the loop is maintained as nearly as possible between 0 and 2° C. Apprehension was felt at first that the pressure of the ligature might cause necrosis of the bowel or thrombosis of its vessels, but, although this danger is real, it is minimized when the refrigeration includes not only the asphyxiated loop but also a narrow zone above the ligature.

A considerable series of experiments were first performed upon rats, with ligation of various lengths of intestine for various periods of 2 to 6 hours. It was easily established that the intestine after such treatment with refrigeration retains excellent color and tone without signs of gangrene. The mortality, however, was very high, evidently from chilling and exhaustion, in spite of attempts at artificial warming of the body, because the blood counts gave no indication of shock but the body temperatures fell very low. Larger animals, therefore, were used for continuing the experiments. The records shown in the table are illustrative.

Dr. A. S. Price kindly provided the following additional data for the blood of Cat D on the day of death; differential: large and small lymphocytes, 22 per cent; mature polymorphs, 60 per cent; immature polymorphs, 18 per cent; blood sugar, 98; urea, N 56, NPN 85; plasma, NaCl 480 mg. per cent.

At autopsy the heart and great veins of this cat were full of blood. Lungs were normal. Liver was moderately congested. Other viscera, including spleen and bone marrow, were grossly normal. Stomach was tightly contracted and empty except for a little pale yellow fluid; there were also signs of vomiting of such fluid. The perito-

neum was free from exudate, its surfaces glistening, not inflamed. The intestine was empty throughout except for a trifle of fluid like that in the stomach and completely free from adhesions; the walls were firm and moderately contracted, completely free from signs of necrosis, inflammation, or edema. The gall bladder contained about 1 c.c. of turbid light yellow bile. A small amount of urine was free from sugar, acetone, and albumin. The brain and spinal cord were negative to inspection.

Microscopic report from Dr. Price: Lungs, pancreas, adrenals, thyroid, and parathyroids were essentially normal. There was simple passive congestion of liver, without fatty changes; slight lymphocytic infiltration in some portal canals; small amount of yellow pigment suggesting hemosiderin, chiefly within some of the hepatic cells, also in some Kupffer cells. Other sections of liver showed some simple toxic degenerative changes with beginning necrosis. Kidneys: no evidence of true nephritis. Glomeruli were moderately congested but well preserved. There was marked cloudy swelling and some degeneration in tubules; either hydropic or fatty vacuolation of cells in convoluted tubules; several focal areas of lymphocytic and monocytic infiltration in cortex. Spleen appeared somewhat collapsed, with prominence of muscle trabeculae and obliteration of follicles, with fibrosis where some follicles should be. Stomach was normal. Duodenum showed some cloudy swelling of the muscle fibers. "Sections from the intestinal wall show some loss in goblet cell formation, slight increase in acidophilic staining of the cells, and simple degenerative changes in the epithelium. There is no evidence of any marked degree of exudative peritonitis, although some sections do show the submucosa presenting an increase in lymphocytic infiltration in the perivascular areas." Smears of the marrow from femur and ribs appeared normal. The abdominal lymph glands showed some edema and congestion, with small areas of necrosis surrounded by reticuloendothelial hyperplasia. No blood cultures were taken.

Several other attempts of this kind gave the same type of result with still earlier deaths. Likewise, several trials with ligation of special portions of the intestine (upper part for endocrine possibilities, lower part for fecal absorption, etc.) proved fatal, partly or wholly because of the poor facilities.

OBSERVATIONS ON PERITONITIS

Two results of the work with intestinal ligations require additional mention:

1. The experiments were all performed with shaving or plucking of only a small area of the abdomen and with no attempt at asepsis; nevertheless, with all the ligations, of all durations up to 16 hours, symptoms or signs of peritoneal infection were never encountered. Although the rat and rabbit have very high natural resistance, the cat is reputed to be fairly susceptible to peritonitis. In the absence of controlled proof there is a possibility that the refrigeration and ligation may increase the local resistance, perhaps through the ensuing hyperemia. It at least seems certain that this treatment does not seriously lower the peritoneal resistance.

2. Adhesions were strikingly absent after all the ligations, except a few in places where the peritoneal surfaces had been considerably traumatized by the ligature. By comparison with a few animals in which the intestine had been similarly handled or ligated for a very

brief time at room or body temperature, the reduction of adhesions by cold seemed definite and positive. In particular, the paralysis of the omentum by cold, so that it does not migrate or cling in the usual manner, is visibly evident during and after refrigeration. It seems probable that cold completely prevents the immediate formation of adhesions and thus allows slightly injured organs to repair themselves without forming attachments, but it does not prevent the later formation of adhesions when surfaces are too badly injured or stripped of peritoneal covering.

Several experiments were performed, without ligation, chiefly in rats by packing the peritoneal cavity with ice or irrigating it with iced saline solution while the animal was suspended in a warm bath to keep up the general body temperature. Also, animals which had developed peritonitis from accidental causes were treated similarly, with or without the use of antiseptics in the peritoneum, with the idea that the cold might retard the absorption of either toxins or chemicals. Cleansing of the peritoneum, which is considered practically impossible, might thus become feasible and the subsequent hyperemia conceivably might increase resistance. Though this work was not thorough or conclusive, it gave the impression that the method is useless because the infection is in the peritoneal tissue and not merely on its surface and also that the manipulations are harmful.

The same conclusion was reached in an experiment with a pure culture of *Staphylococcus albus,* selected as an organism of low virulence. The growth from one agar slant was emulsified in 30 c.c. of saline solution and divided in two lots of 15 c.c. each. These were injected intraperitoneally in two cats. Both vomited and were somewhat unwell within one-half hour. Laparotomy then was performed under amytal and a little ether. The spleen and entire intestine of one cat were brought out into a bowl of saline solution at about 38° C. and washed gently for ten minutes. The spleen and intestine of the other cat were similarly eventrated, their circulation cut off by long elastic clamps, and they were first painted with mercurochrome and then washed for ten minutes in successive bowls of iced saline solution. Both wounds were closed immediately after the treatment. The first cat recovered with scarcely any symptoms. The second died after three days with the abdomen full of white staphylococcal pus.

Though the resistance was evidently lowered by this treatment, it must be noticed that the entire peritoneum was infected, including parietal and other surfaces not included in the ligation and refrigeration, and these parts might have been affected injuriously. It was intended to perform other experiments more strictly localized, in which the eventrated bowel would be suspended in an iced bacterial suspension during ligation, but under the circumstances these could not be carried to any positive conclusion.

The salient point established is that ligation combined with refrigeration seems to have a powerful effect in preventing shock, toxic absorption, and formation of adhesions, as well as maintaining the vitality of the tissues. It, therefore, might offer a promise of clinical usefulness in cases of extensive wounds or infections involving the intestine, if the single serious objection could be obviated. This obstacle is the fatal cachexia and anemia which have followed refrigeration of the entire intestine. Further experiments must decide whether this condition is due only to the crude methods necessitated by the lack of facilities, whether it is peculiar to cats or whether it represents a special disturbance of metabolic or other unknown character.

CONCLUSIONS

1. Animals have survived the ligation and refrigeration of short loops of intestine for as long as 16 hours and of half of the small intestine for 4 hours.

2. Among the noticeable results at the end of such treatment are the rosy pink color and very firm tone of the intestine. Microscopically the walls show edema and some infiltration for a time, but there are no clinical symptoms of either obstruction or paralysis at any stage.

3. The formation of adhesions seems to be largely inhibited, though denuded areas necessarily form attachments later.

4. Resistance to peritoneal infection seems not to be lowered and may possibly be increased.

5. Some degree of cachexia and anemia follows every severe procedure of this kind. These have proved fatal in all experiments with ligation of the entire intestine. If further investigation proves this to be a specific disorder, it may possibly prove of interest to students of anemia.

6. If this difficulty can be removed, the method described may possibly become useful in certain surgical cases.

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EXPERIMENTAL ATTEMPTS TO PREVENT OR ABOLISH THE HYPERTENSION THAT IS ASSOCIATED WITH RENAL ISCHEMIA

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AN INGENIOUS method for the production of persistent hypertension in dogs has been described by Goldblatt and his associates.[1] It consists of constricting the main renal arteries by means of special silver clamps devised for the purpose. Many different experiments by various workers have been and are being performed in an effort to explain the mechanism of this type of hypertension. Much of the work has been reviewed recently by Goldblatt[2] and by us.[3] The prevailing evidence at present indicates that this type of experimental hypertension is due primarily to a humoral and not to a nervous mechanism initiated by ischemia of the kidneys. The nature of the hypothetical substance responsible for inducing the hypertension has not yet been determined.

The present paper deals with experiments in which an attempt has been made to gain additional information concerning the mechanism whereby renal ischemia induces the development of hypertension.

METHODS AND RESULTS

Seven different types of experiments were performed. The method which was used for the blood pressure determinations consisted of puncturing the femoral artery with a needle that was connected to a mercury manometer.

I. *The Effects on the Blood Pressure of Connecting the Renal Vein to the Portal System Prior to Constriction of the Renal Artery.*—One of the prevailing theories in regard to the etiology of experimental renal hypertension is that the ischemia is associated with the formation of a pressor substance which, when liberated into the blood stream, causes a rise in the blood pressure. These experiments were performed in order to test the possible rôle of the liver in removing this hypothetical substance from the blood. Through an incision in the left flank, the splenic and renal pedicles were exposed. The left renal artery was occluded temporarily by a bull-dog clamp. The splenic and renal veins were divided and the distal end of the renal vein was anastomosed to the proximal end of the splenic vein, thus forcing a large part of the blood from the kidney to return to the heart by way of the liver. The clamp was removed from the artery and the incision was closed. These procedures alone at times resulted in a temporary rise in the blood pressure. Several

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days later, the right kidney was removed. After allowing the animal to recover from this operation, the left renal artery was partially occluded by a Goldblatt clamp.

Eleven experiments of this type were attempted but all except four were failures for various reasons. A rise in the arterial blood pressure occurred following the production of renal ischemia in the four experiments. The elevation in pressure was of approximately the same degree as one would have anticipated had the renal blood been emptying normally into the inferior vena cava instead of into the portal system.

II. *Effects of Renal Ischemia on Blood Pressure After Having Damaged Kidneys by Temporarily Blocking Renal Veins.*—It seemed possible, although unlikely, that severe damage to the kidneys might alter the response to a diminution in their arterial supply. For this reason, the renal veins of four dogs were completely occluded for an average period of four hours. A number of days separated the occlusion of the veins of the two kidneys. One of the animals developed a temporary rise in arterial pressure following these procedures alone. Following the recovery of the animals, the renal arteries were partially occluded by Goldblatt clamps, and all of them showed a definite rise in the arterial blood pressure. Except for some diminution in their sizes, the kidneys appeared essentially normal at autopsy.

III. *Effects of Constriction of Renal Veins After a Rise in Blood Pressure Had Been Produced by Partial Occlusion of Renal Arteries.*—It has been shown[4] that constriction of the renal arteries to the degree that results in hypertension is associated with a diminution in the renal blood flow and with a decline in the pressure in the renal arteries. It was thought that the rise in pressure in the kidney vessels which would be associated with constriction of the renal veins might result in a decline in the general arterial blood pressure. In two animals in which hypertension had followed partial occlusion of the renal arteries, the renal veins were constricted with Goldblatt clamps. The arterial blood pressure rose slightly in one experiment and declined slightly in the other, but the changes were no greater than those frequently encountered in this type of hypertension.

IV. *Effects of Constriction of Artery to Remaining Kidney When Adrenal Gland on That Side and Kidney on Opposite Side Have Been Removed.*—It has been shown[2, 3] that bilateral adrenalectomy prevents or abolishes hypertension due to renal ischemia. Cow[5] described a direct vascular connection between the medullary portion of the adrenals and the kidneys. He stated: "Under certain conditions adrenalin in appreciable amount is poured directly into the kidneys from the suprarenal bodies, producing a diminution in the flow of urine." It was concluded by Cow that the adrenals may be regarded as direct regulators of urinary activity. Since constriction of the renal artery results in a reduction in the pressure distal to the clamp and since the arteries to the adrenals are concerned in the collateral arterial circula-

tion that develops, it seemed possible, although unlikely, that the removal of the adrenal on the side of the remaining kidney might influence the response to renal ischemia.

Four experiments were performed in which the right kidney was removed, the left adrenal gland was removed, and, either immediately or several days later, a Goldblatt clamp was placed on the left renal artery. A definite rise in blood pressure occurred in all instances.

V. *Effects of Freeing Adrenals Except for Small Attachments Along Renal Pedicle on the Hypertension Associated with Renal Ischemia.*—As stated, it has been shown that bilateral adrenalectomy prevents or abolishes hypertension due to renal ischemia. Goldblatt[2] found that an amount of cortex without medulla close to the minimum requisite for survival still permitted the development of hypertension due to renal ischemia. The present experiments were performed in order to determine if a marked reduction in the blood supply to the adrenals would abolish the hypertension associated with renal ischemia.

Six experiments were performed on dogs with hypertension in which the adrenal glands were freed except for their attachments along the renal pedicle. Little if any alteration in the blood pressure followed this operation. Subsequently in several instances the adrenals were completely freed of all attachments and the blood pressure declined markedly.

VI. *Effects of Renal Ischemia on Blood Pressure When One Adrenal Has Been Removed and the Other Adrenal Has Been Completely Denervated by Transplanting It to the Neck.*—It has been noted previously[3, 6] that constriction of the artery to a kidney which has been denervated by transplantation results in an elevation in the blood pressure. As stated, renal ischemia is not associated with hypertension if both adrenal glands are removed. The present experiments were performed for the purpose of determining whether or not renal ischemia will result in hypertension if the adrenal glands are denervated. The most obvious manner of accomplishing this appeared to be to transplant one adrenal to another part of the body, such as the neck, and subsequently to remove the other adrenal. This method will be described subsequently but suffice it to state here that the adrenal was transplanted together with the adjacent kidney and this kidney was removed later leaving the adrenal in the neck. Following the removal of the nontransplanted adrenal, a Goldblatt clamp was applied to the artery of the remaining kidney.

Three experiments of this type were performed. In each instance a definite elevation in blood pressure was noted following the partial constriction of the artery to the remaining kidney. The results of an individual experiment follow and the blood pressure readings are given graphically in Fig. 1.

PROTOCOL.—Large, male dog. Control blood pressures on Nov. 8, 9, and 10, 1937, were approximately 130 mm. Hg. Nov. 11, ether anesthesia, left kidney and adrenal

transplanted to neck. Organs without blood supply for thirty-five minutes. Blood pressure remained at essentially preoperative level. Dec. 13, right adrenal gland removed. Animal's condition remained about the same; blood pressure not altered. Dec. 20, transplanted kidney removed under local anesthesia, leaving left adrenal in neck. Condition of animal continued to be good, blood pressure unaltered. Jan. 19, 1938, right renal artery constricted by Goldblatt clamp, 1⅛ of 3⅘ turns. Jan. 21, blood pressure 148; Jan. 24, blood pressure 172; Jan. 26, blood pressure 185; Jan. 29, blood pressure 184; Jan. 30, blood pressure 200; Feb. 2, blood pressure 220; Feb. 3, blood pressure 236; Feb. 4, blood pressure 215 mm. Hg, dog vomited; Feb. 5, blood pressure 225; Feb. 7, blood pressure 230, dog quite sick, vomiting, convulsions, definite uremia, killed. Renal artery blocked at site of clamp by organized thrombus. Kidney appeared fairly normal. The transplanted adrenal was essentially normal both on gross and microscopic examination.

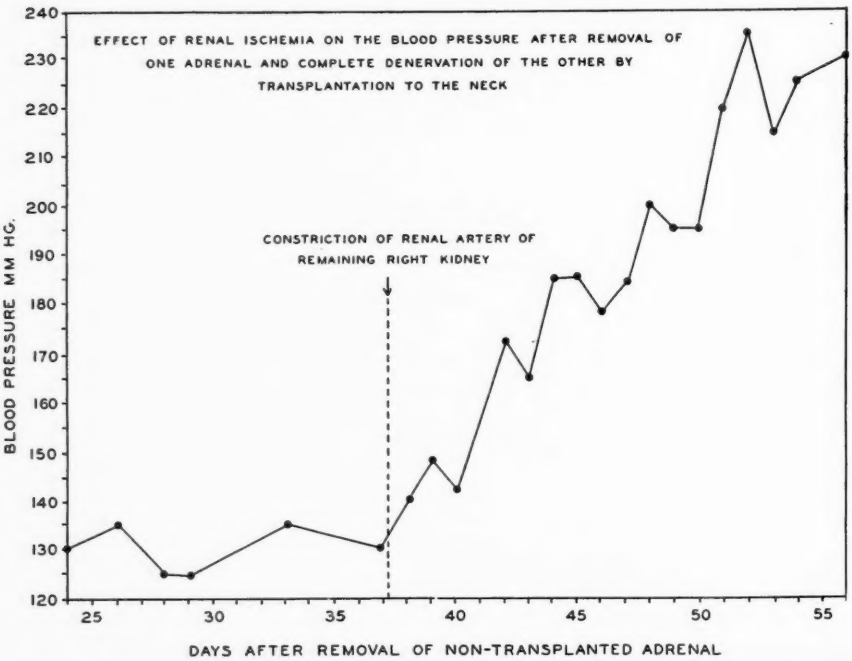

Fig. 1.—Showing the effects of renal ischemia on the blood pressure when one adrenal and one kidney have been removed and when the remaining adrenal has been transplanted to the neck.

VII. *Attempts to Abolish Renal Hypertension by Fever Therapy.*—We have the definite impression that it is more difficult to produce hypertension in dogs which are not in the best of physical condition than it is in entirely normal ones. Animals with nasal discharge and other evidences of distemper rarely respond with much elevation in blood pressure following constriction of the renal arteries. On a number of occasions, it has been noted that the elevated blood pressure of a dog with renal ischemia declines if the animal develops distemper. Further, the decline was replaced subsequently by a rise in pressure in some instances when the animal recovered from the distemper. If a dog with hypertension developed severe mange or a virulent infection of any type, there was usually a decline in the blood pressure.

One of the findings in distemper is an elevation in the temperature, and it was thought that the fever might be responsible for the decline in blood pressure that had been observed in some of the animals. For this reason, the effects of hyperpyrexia were studied. The two methods chosen for producing artificial fever were (1) exposure to an atmosphere with an elevated temperature and (2) the injection intravenously of 0.5 to 1.5 c.c. "double strength" typhoid vaccine. Three animals with hypertension were placed each day for from five to ten days in the warm compartment. The daily exposure was for approximately four hours. The temperature of the animal at the end of this time varied from 104 to 107° F. and there was usually a temporary decline in the blood pressure of from 10 to 20 mm. Hg. However, this decline was only temporary and it returned by the following morning to its previous level. A sustained reduction in the blood pressure was not encountered in the three experiments. The same was true in the one experiment in which hyperpyrexia was caused by injecting typhoid vaccine.

SUMMARY

The results of experiments which were performed in an attempt to prevent or abolish the hypertension that is associated with renal ischemia are reported. Partial constriction of the renal artery or arteries was common to all experiments. Efforts to influence the response to renal ischemia included (1) anastomosis of the renal vein to the portal system, (2) previous damage to kidneys produced by temporary occlusion of renal veins, (3) partial constriction of renal veins in presence of hypertension, (4) removal of adrenal gland on side in which renal ischemia is produced, (5) the freeing of the adrenal glands except for small attachments along the renal pedicle, (6) removal of one adrenal and denervation of remaining one by transplanting it to the neck, and (7) hyperpyrexia. All of these attempts were unsuccessful in altering the response of the blood pressure to renal ischemia. A severe illness such as distemper is usually accompanied by a decline in the elevated blood pressure that is associated with experimental renal ischemia.

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THE PATHOGENESIS OF SEMINOMA OF THE TESTIS

A Histologic Study in Dogs

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THERE has been considerable difference of opinion in the past as to the origin of the testicular tumor which is variously called "seminoma," "embryonal carcinoma," "spermatocytoma," and "round cell sarcoma." Spontaneous seminomas in dogs are suitable for such a study as this, not only because their histologic appearance is identical with that of such tumors in man, but because, in dogs, seminomas are often found in an early stage of development. Among tumors of the human testes, it is unusual to find a seminoma which is not diffuse.

Langhans, in 1887, suggested that carcinoma of the testis arises from tubules in the region of the rete. He described the transition in certain early cases from glandular formation to solid tumor. Chevassu, in 1906, studied 128 tumors of the human testis. He separated fifty-nine of these tumors from the teratoid group and called them "epithelioma seminal" or "seminome." He considered the various elements in the testis from which they could arise and decided that the most likely structure of origin was the seminiferous tubule. He felt that the spermatogenic elements in the tubule were the ones involved in the process rather than the supporting or Sertoli cells. Bell (1925) regarded the seminoma as a specific tumor of spermatogenic origin. In certain specimens he was able to find histologic characteristics in various tubules adjacent to the tumor which he felt were evidences of hyperplasia. From these tubules he could trace the transition to a gross infiltrating seminoma. He divided seminomas into a subgroup of carcinosarcomas in which he believed that both sarcomatous and carcinomatous elements were blended.

Ewing (1928) believed that seminomas were merely a carcinomatous development in teratomas. He felt that if one sectioned these tumors sufficiently teratomatous structures frequently could be demonstrated. Ewing disagreed with the interpretation that Bell placed on the histologic picture showing the transition from normal tubules to seminoma. Ewing regarded this appearance as either one of benign hyperplasia or actual invasion of the tubules with tumor from the main mass.

Broders (1932) studied the problem of epithelial hyperplasia as opposed to early carcinoma. He stated that "the day has passed when

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epithelium can be considered noncarcinomatous or at the most only precarcinomatous because it is within the confine of the so-called basement membrane." He recognized this change as occurring in both squamous and glandular epithelium and called it "carcinoma in situ."

Bouffannais (1929) reported the occurrence of a typical seminoma in an old dog. He observed that the tumor was of multicentric origin ("la genese pluricentrique"). Peyron (1936) noted that seminomas in dogs often confined themselves to the tubules. Peyron, Blanchard, Drieux, and Salomon (1936) remarked on the similarity between seminomas in human beings and dogs. They divided seminomas into two types—the seminal and the Sertoli cell type. The Sertoli cell type differed from the usual seminoma by forming good glandular structure. Deitermann (1937) studied twenty-seven cases of seminoma of the human testis, and was unable to demonstrate teratomatous tissue in any of them. Ectopic testes in the human have been regarded as particularly prone to the development of tumors.[10] This dictum would appear to be true for dogs also. Greulich and Burford (1936) reported three seminomas of the cryptorchid testes of dogs.

MATERIAL

This study is based on 25 cases of spontaneous seminoma. These tumors were an incidental finding at post-mortem examination of dogs except in 1 case in which the tumor had metastasized and was the contributory cause of death. The involved testes were fixed in formalin; paraffin sections were cut on the entire testis and stained with hematoxylin and eosin.

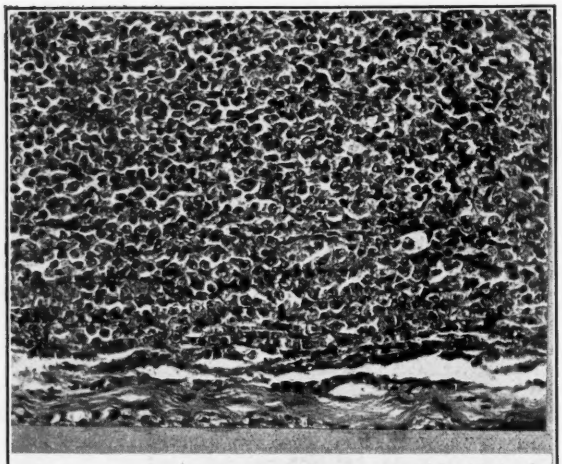
These 25 seminomas were found in 22 dogs, in 3 of the animals the tumors being bilateral. Four seminomas were present in cryptorchid testes, in 1 dog a seminoma being present in each testis. On gross examination, testes containing seminomas were usually found to be enlarged, although a small proportion was found on routine sectioning in testes that grossly appeared perfectly normal. In those specimens in which the tumor was infiltrating, it appeared as a grayish mass of firm consistency.

HISTOLOGIC FINDINGS

Histologically, the seminomas were found to consist of cells that had large nuclei and prominent nucleoli, which stained deeply with basic stains. There was little cytoplasm around the nuclei. Mitotic figures were numerous. The most striking feature was the uniformity of the cellular picture, the cells varying little in size and shape (Fig. 1).

In 18 of the 25 seminomas it was apparent that the tumor had arisen from many foci in the seminiferous tubules rather than from a single focus (Figs. 2, 4, 6, and 7). In this group, the tumor was either wholly or partially in situ (Fig. 3). In 14 of these tumors the malignant cells

Fig. 1.



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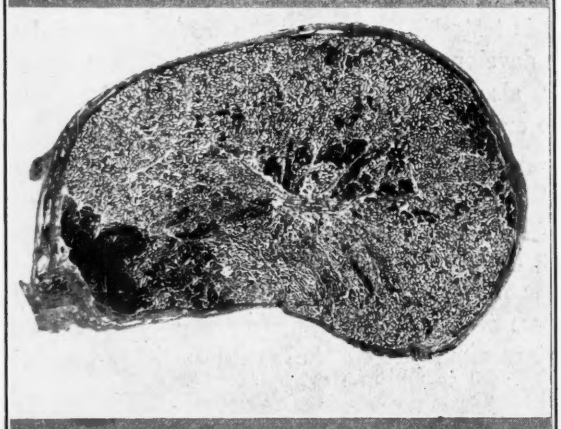

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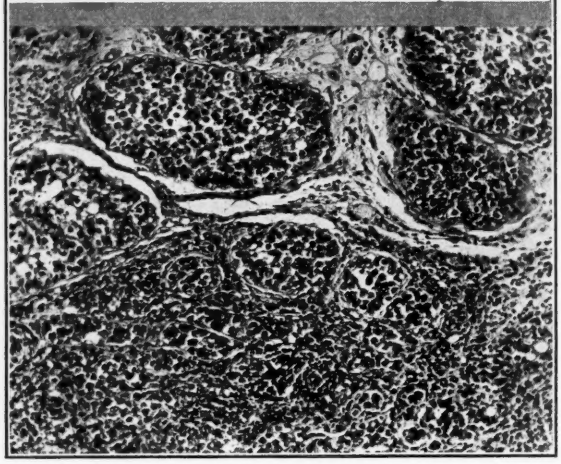
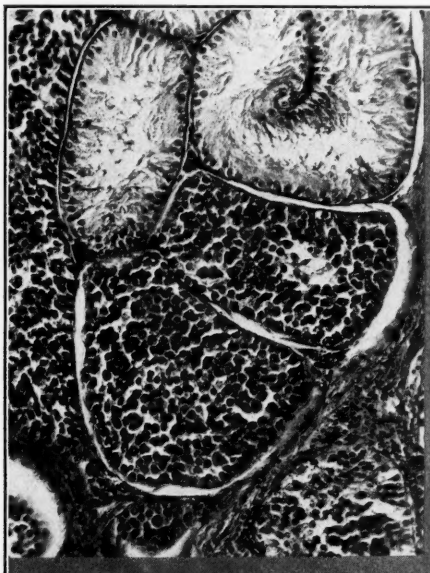


Fig. 1.—Seminoma of testis of a dog, showing marked uniformity in the cellular picture (hematoxylin and eosin, ×205).

Fig. 2.—Seminoma of testis of a dog; the darker areas represent tumor, the multicentric origin being clearly shown (hematoxylin and eosin, ×2½).

Fig. 3.—Seminoma in the cryptorchid testis of a dog; a portion of the tumor is still in situ, whereas the remainder is diffuse (hematoxylin and eosin, ×125).

Fig. 5.



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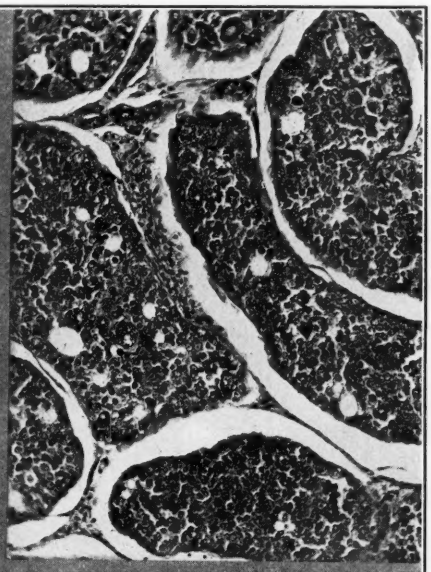

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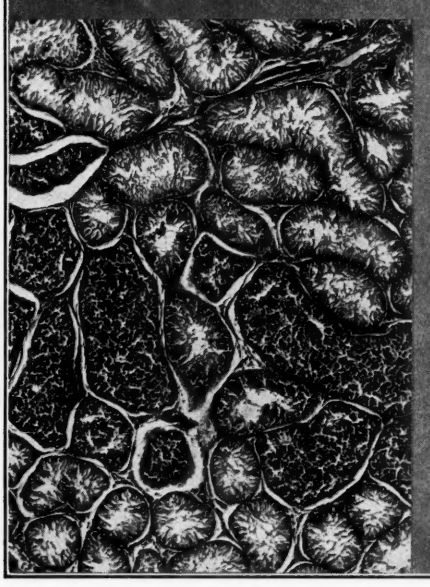

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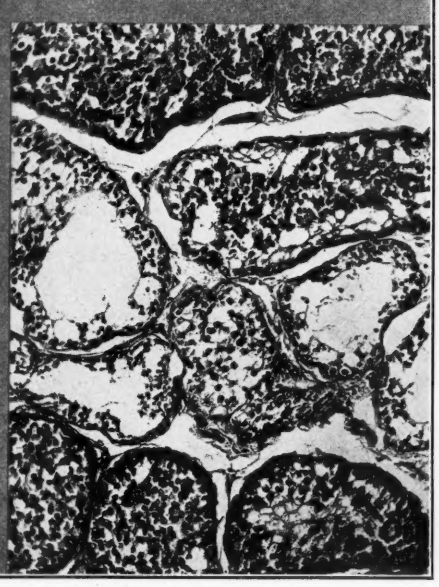

Fig. 4.—Seminoma in the cryptorchid testis of a dog; the multiple foci of origin are shown. The tumor is entirely in situ. The atrophied tubules are contrasted with those filled with tumor cells (hematoxylin and eosin, ×60).

Fig. 5.—Seminoma of testis of a dog; a higher magnification of Fig. 4. The tumor cells are confined to the tubules (hematoxylin and eosin, ×135).

Fig. 6.—Seminoma of testis of a dog; the normal tubules are contrasted with those containing tumor cells which are still in situ (hematoxylin and eosin, ×125).

Fig. 7.—Seminoma of testis of a dog; the tumor is entirely in situ and the tumor cells have an appearance identical with that found in diffuse seminoma (hematoxylin and eosin, ×125).

had not broken through the confines of the so-called basement membrane at any point and so were entirely in situ (Figs. 4-7). In this group the seminomas were in a very early stage of development and had not begun to infiltrate. In the remaining 7 cases, the seminomas were in a much more advanced stage of development and were diffuse. In them the multicentric characteristics, as well as evidence of their origin in the seminiferous tubules, were no longer demonstrable. The cells in the tubules in these cases in which the tumor was in situ were unquestionably malignant; they contained numerous mitotic figures typical of those found in diffuse or metastatic seminoma.

The transition from the normal seminiferous tubule to one filled with malignant cells could be followed in the group of tumors which were still in situ. In the same microscopic field it was possible to find normal tubules adjacent to some which showed early malignant change and to others which were composed entirely of tumor. One early change was the suppression of the formation of spermatids and spermatozoa in the seminiferous tubules. The malignant cells could be traced from the spermatogenic series of cells, apparently the spermatocytes. Normal spermatogonia and Sertoli or sustentacular cells could be demonstrated in many of the tubules in which the seminoma was early and still in situ. The Sertoli or supporting cells could be recognized by their large pale nuclei and prominent nucleoli. The spermatogonia, germinal cells of the spermatocytic series, had smaller nuclei than either the Sertoli cells or spermatocytes, and the nuclei stained very deeply with basic dyes because of clumps of chromatin material (Fig. 8).

Since seminomas originate in the cells of the seminiferous tubules, they are adenocarcinomas or, more specifically, spermatocytomas. All the tumors in this group were highly undifferentiated and were graded 4 according to method of grading tumors used by Broders (1925). Only one seminoma had metastasized. This would emphasize the fact that most of the tumors studied were extremely early.

Seminomas were unassociated with other tumors in 17 instances. Five seminomas were associated only with interstitial cell tumors (Fig. 9); whereas, a seminoma, an interstitial cell tumor, and a grade 1 adenocarcinoma of the so-called Sertoli cell type, were associated in the same testis 3 times.

The average age of the dogs in which seminomas were found was slightly more than 10 years. Most of the testes in which the seminomas were present showed active spermatogenesis. There was, however, no formation of spermatids or spermatozoa in the cryptorchid testes. Two of the scrotal testes in this series presented focal atrophy of the seminiferous tubules.

COMMENT

In those specimens in which the tumor was in situ, it was possible to trace the malignant cells directly from the spermatocytic series of cells

of the seminiferous tubules. This is in agreement with Chevassu's original idea. The objection that such an appearance in the tubules may represent hyperplasia cannot be applicable to this group because the cells in the areas where the seminoma was in situ had a histologic appearance identical to that of metastasis from a seminoma. Furthermore, the idea that these areas of tumor cells within the tubule represented invasion of the tubules from the main tumor cannot be maintained because

Fig. 8.

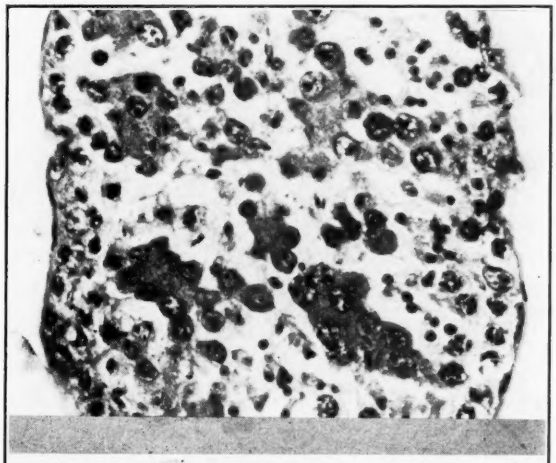

Fig. 9.

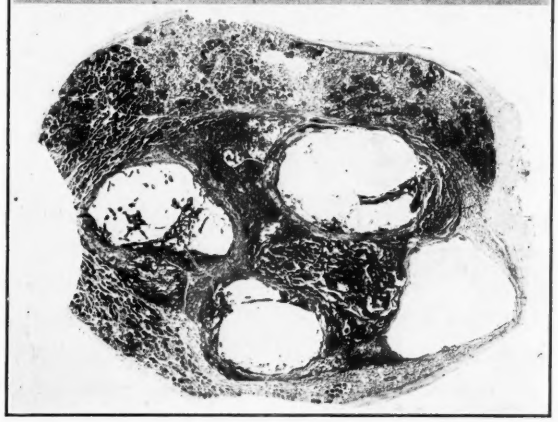

Fig. 8.—Portion of a seminiferous tubule with early seminoma entirely in situ. There are many mitotic figures. Adjacent to the so-called basement membrane, the Sertoli or supporting cells with their large pale nuclei, and the spermatogonia with their small, deeply stained nuclei, can be recognized and are not involved in the malignant process (hematoxylin and eosin, ×425).

Fig. 9.—Seminoma associated with an interstitial cell tumor in the testis of a dog: In the center of the testis there is a large interstitial cell tumor which has undergone hemorrhagic degeneration. Around this tumor there is a seminoma which is entirely in situ. The multicentric origin is shown. The paler staining areas represent normal tubules (hematoxylin and eosin, ×3).

in more than one-half of the specimens examined the tumor was entirely in situ. It seems probable that the majority of seminomas originate in multiple foci. When, however, such foci coalesce, it is no longer possible to make such an observation. This was the case in 7 seminomas of this

series and is the usual finding in specimens of seminoma of the human testis. When seminomas do become diffuse, with fusion of the various points of origin, it is impossible to demonstrate their origin because they are of such a high grade of malignancy that there is no differentiation into tubules.

It has been shown by various observers that the ectopic testis is more susceptible to the development of tumor than the scrotal testis. This would appear to be true for the dog.

Seminomas were found in animals having an average age of about 10 years. The majority of seminomas in human beings are found between the ages of 35 and 45 years (Chevassu). A comparison of the age incidence of this tumor in human beings and dogs shows that in the dog it occurs in a relatively similar age span. It would appear that seminomas are of relatively more frequent occurrence in dogs than in human beings. However, accurate statistics are not available.

It has been suggested (Peyron, Blanchard, Drieux, and Salomon) that seminomas be divided into the seminal type and Sertoli cell type. To include the latter in the classification does not seem to be justified because Chevassu, in his original description, included only the seminal type. Furthermore, the seminal type usually is of grade 4 malignancy, whereas the Sertoli cell type is almost invariably of grade 1 malignancy. This Sertoli cell type has also been described in the literature as adenoma (Chevassu, Ewing). The four tumors which have been seen in this group are more fully described elsewhere.

SUMMARY

Twenty-five seminomas of testes of dogs have been studied. Eighteen of these seminomas were in an early stage of development, being still in situ. In this group it was demonstrated that the tumor arose from multiple foci in the seminiferous tubules. The malignant cells could be traced directly from the spermatogenic series of cells. All the seminomas in this group were regarded as being adenocarcinomas of grade 4 malignancy.

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Erratum

In the article by Dr. F. Gregory Connell entitled "Partial Gastrectomy in Treatment of Peptic Ulcer," which appeared on page 696 of the May issue, Fig. 1 was printed upside down. It is reprinted here in its proper position.

Fig. 1.—Shift to left in gastric resection

Editorials

Recent Advances in Our Knowledge of Biliary Function

THE CONTRIBUTIONS of fundamental science to our knowledge of the physiology and pathologic physiology of the biliary apparatus have had a profound influence on the preoperative preparation and postoperative care of patients with biliary tract disease. The work of Rous and his associates gave new impetus to a study of this system and resulted in a better understanding of the processes involved in disease of the liver and bile passages.

The brilliant researches of Mann and his associates provided new knowledge on the functions of the liver. The important part which this organ plays in carbohydrate, protein, and fat metabolism is being more clearly elucidated. The intermediary metabolism of these foodstuffs, in which the liver plays no insignificant role, is now being elaborated. Only recently the liver has assumed a more important role in the mechanism of production of diabetes mellitus, whether or not one accepts the view that "overproduction" of glucose and fat is the primary factor in this disease. The investigations of Best and his coworkers have added greatly to our knowledge of the liver lipid metabolism.

It is unfortunate, but true, that during this period of intense investigation into the problems of hepatic physiology an attempt has been made to apply the results of these researches to clinical evaluations of hepatic function. In an organ whose known functions require but a small portion of normal liver tissue for their normal activity, the majority of these tests were doomed to failure from the beginning. The carbohydrate metabolism of the liver can be adequately carried on with only 20 per cent of normal tissue, and deaminization with even less than this. The dye tests are without doubt of some value and the more recent work of Quick on hippuric acid conjugation has real possibilities. These tests are at present the only methods of real value in clinical practice. When, however, such conditions as anoxemia, anesthesia, hemorrhage, trauma, and infection, which are daily met in surgical practice, can convert a completely normal liver, as determined by the tests now available, into a completely incompetent organ, we must look with prejudice at those tests which give evidence of normal activity of the liver when a major portion of the organ has already been destroyed.

The recent observations of Goldschmidt, Vars, and Ravdin on the conditioning effect of liver fat on liver necrosis following the administration of volatile anesthetics explain, in part at least, the value of a high carbohydrate diet in patients with serious hepatic disease. The work of Forbes and Neal on the protective action of xanthine against the liver necrosis which follows the administration of chloroform or carbon tetrachloride, while not clearly understood, provides another link in our knowledge of the methods by which protection can be afforded the liver.

It is now generally accepted that the gall bladder is not a vestigial structure, that it does have an important function which is destroyed when it is injured by infection or disease. The contributions of Graham, Cole, Schönheimer, Ivy, Johnston, Riegel, Andrews, and Ravdin have added greatly to our knowledge of normal and pathologic function of this viscus. The investigations of these, and many other workers, have offered more valid explanations of the pathologic physiology of the extrahepatic bile passages and have provided a more reasonable explanation for the persistence of symptoms in patients operated on for gallstone disease.

Less than twenty years ago one of the most brilliant of American surgeons stated that the arterial blood supply of the liver was not necessary for the maintenance of normal hepatic function: "Physiologists point out that the hepatic artery furnishes oxygen to the liver, and this would appear to be true, but the supply is not sufficient to lead us to believe that oxygen is necessary to its function." It is now recognized that the hepatic arterial blood is of the greatest importance in maintaining normal function and that complete ligation of the entire hepatic arterial supply is incompatible with life.

The more recent work on vitamin K and intestinal bile deprivation on the hemorrhagic tendency in obstructive jaundice offers new hope that before long this dreaded complication may be prevented by adequate pre- and postoperative therapy. The alteration in the prothrombin level in obstructive jaundice which has been described by Quick and his associates, and which has now been amply confirmed, provides additional evidence of the important part which fundamental investigations are playing in the better understanding of the problems of the surgical patient.

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Continuous Drip Transfusion

BECAUSE the average blood transfusion of 500 c.c. will only raise the hemoglobin from 8 per cent to 10 per cent and is therefore inadequate to cope with the severe anemias, Marriott and Kekwick[1] have recently advocated the use of massive transfusions slowly administered. The method consists essentially of obtaining blood from a number of donors compatible with the recipient and with each other, adding 3.8 per cent citrate solution as an anticoagulant, and permitting its introduction into the vein of the recipient at the rate of approximately 40 drops per minute or 133 c.,c. per hour. Because of the tendency of the corpuscles toward sedimentation in the reservoir and the consequent blocking of the drip bulb, a stirring action accomplished by bubbling a continuous stream of filtered oxygen through the blood is necessary. The amount of blood transfused is determined by periodic hemoglobin examinations and the transfusion is discontinued when the normal hemoglobin percentage has been restored.

The advocates of this method contend that it is particularly indicated in that group of cases characterized by severe acute anemia with consequent depression of hematopoietic function in which the ordinary single transfusion of 500 c.c. is of relatively little value. In such cases in which the hemoglobin percentage may be reduced to 25 or 30, it is necessary to administer as much as 4 to 5 liters of blood. Obviously, such massive dosages cannot be given in a single transfusion by the customary procedures. Accordingly, the continuous drip method provides sufficient amounts in such a manner as to obviate possible embarrassment to the cardiovascular system and the development of "speed shock." This latter untoward reaction has been popularized by Hyman and Hirshfeld,[2] who concluded from their investigations that rapid introduction into the blood stream of a great bulk of fluid results in a state of shock.

Whereas it is fully agreed that the customary single transfusion of one pint of blood is merely homeopathic in combating such severe anemias, our discordance with the advocates of this method of transfusion is based on certain fundamental physiologic principles. It is inopportune here to enter into a lengthy discussion of the pros and cons of the citrate method of transfusion, but our opinion is succinctly and aptly expressed in the words of Lederer,[3] who states: "The general principle that the more closely the blood introduced into the recipient approximates the blood in its natural condition is a fundamental one. No matter how simple and how easy a method is, if that method permits of changes in the blood due to the admixture of foreign substances, to changes in reaction or temperature, to biological alterations in morphology (coagulation), and to ferment action, it is a departure from this principle." Aside from this rational disadvan-

tage of the continuous drip method, the same therapeutic effects can be accomplished more physiologically and more simply by frequently repeated transfusions of unmodified blood. We have often transfused as much as 5 to 7 liters of unmodified blood in three or four days. Moreover, there has never been any untoward reactions in these cases. As regards the phenomenon of "speed shock," our experience has been similar to that of Milbert[4] and Unger.[5] In well over 5,000 transfusions this reaction has never been observed, and not infrequently as much as 650 c.c. is transfused in three minutes.

Thus, because in our experience the same purpose and advantages claimed for continuous drip transfusion can be obtained by frequently repeated transfusions of unmodified blood and because this latter method is more rational, more physiologically ideal, considerably simpler, and certainly as safe or safer, we find the indications for the continuous drip procedure conspicuously restricted.

—*Michael DeBakey, M.D.*
New Orleans, La.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

MAMMARY TUMORS

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(From the Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University)

IT IS generally stated that a lump found in the breast of a woman who has reached or who has passed sexual maturity is presumably cancer until proved otherwise. Since the mammary gland is frequently the seat of hyperplastic changes and benign tumor formation, this assumption increases the importance but does not simplify the problem of differential diagnosis. The presence of multiple lumps in the breast of women with chronic cystic mastitis during the childbearing period, the appearance of a solitary nodular growth in the postpuberty period, in cases of fibroadenoma, and the occurrence of a nodule near the nipple associated with a sanguineous discharge in cases of intracystic papilloma are relatively common. Together these cases of chronic cystic mastitis, fibroadenoma, and intracystic papilloma are about as frequent as carcinoma. The clinical and pathologic features which aid in distinguishing these benign lesions from carcinoma have become increasingly important, since the campaign of public education in regard to cancer is bringing patients for examination at a stage when the classical symptoms and signs of carcinoma are lacking.

HYPERTROPHY AND HYPERPLASIA

Hypertrophy of the Mammary Gland.—Hypertrophy of one or both breasts occurs in both males and females and is more easily distinguished from carcinoma (because of the diffuse enlargement of the gland) than mammary hyperplasia in chronic cystic mastitis, which results in the formation of one or more nodules. Enlargement of the breasts in female infants, accompanied at times by menstruation, is found in cases of sexual precocity. The most common cause of such instances of infantile mammary hypertrophy is a granulosa cell tumor of the ovary. Rarely, the precocity may be produced by a pituitary disturbance and anterior pituitary-like hormone in the form of prolan can be demonstrated in the urine. In such cases the pituitary activity stimulates the formation of follicular cysts in the ovary lined by granulosa and theca lutein cells which secrete estrin and bring about the

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mammary development. In the cases of granulosa cell tumor an increased secretion of estrin is also responsible for the abnormal growth of the breast. That hypersecretion of estrin may be the causative factor is suggested by the production in girls of infantile hypertrophy after the injection of this hormone when it is used in the treatment of gonorrheal vaginitis (Fig. 1).

In girls at puberty breast development may greatly exceed the normal in one or both breasts. Asymmetrical enlargement of the breasts between the ages of 10 and 13 years usually corrects itself by the end of puberty. In cases where the enlargement continues to abnormal size, the exaggerated breast development is the result of excessive

Fig. 1.—Infantile hypertrophy of the breast, in a girl aged 2 years. The patient had been menstruating since the age of 3 months and had both pubic and axillary hair and a positive Aschheim-Zondek test in the urine. The condition was apparently produced by overactivity of the anterior lobe of the pituitary.

amounts of duct and periductal tissue similar in other respects to that found in normal puberty. There are thirty-three such cases recorded in this laboratory. In these cases there is apparently an increase in the blood level of estrin and an increased susceptibility of the breast to this ovarian secretion. Virginal hypertrophy once established tends to persist (Fig. 2). To date we have had no encouraging results from endocrine therapy, and surgery is indicated where the enlargement is excessive. In about one-tenth of the cases a localized fibroadenoma will be found in one of the enlarged breasts. This occurred in a patient reported by Johnson and Bloodgood in 1906. Enlargement of the breasts approaching virginal hypertrophy and known as gravid hyper-

trophy may be seen in women who have borne their first child, persisting after lactation but having its onset during pregnancy.

Gynecomastia.—Gynecomastia in the male is the homologue of virginal hypertrophy in the female (Fig. 3). Slight and transient enlargement of the breast at puberty is a normal occurrence in a definite percentage of males. Jung and Shafton found temporary enlargement in 36 per cent of boys between 12 and 13 years and in 77 per cent between 13 and 14 years. One or both breasts may be diffusely enlarged and the condition persistent, either at puberty or with the decline of sexual life. The benign enlargement, as in infantile or virginal hypertrophy in the female, is the result of increase in the length of ducts and in periductal connective tissue. Clinical observations indicate a definite relationship

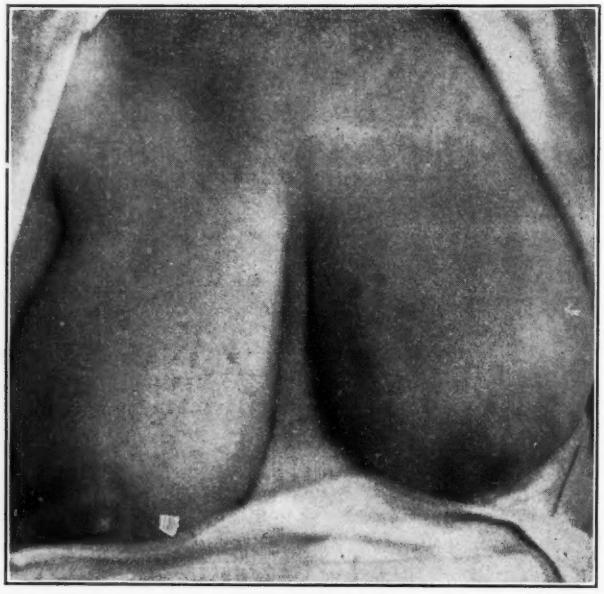

Fig. 2.—Virginal hypertrophy beginning at the age of 13 years before the onset of menstruation. These breasts are unusually sensitive to estrin stimulation.

between the sex organs and gynecomastia (Lewis and Geschickter). Enlargement of the male breast is observed in hermaphrodites. This condition occurs in 5 per cent of the cases of chorioepithelioma or teratomas of the testicle (Ferguson). In boys or young adults excision or atrophy of one testicle with hypertrophy of the interstitial cells of the opposite testicle may lead to mammary enlargement. Moehling has reported cases of hypophyseal tumors in men with enlargement of the breast. The chorionic tissue present in testicular tumors has been found to secrete both prolan, the pituitary-like sex hormone, and estrin, the female sex hormone. Injections of estrin alone will produce this gynecomastia in male monkeys and in humans. Apparently, therefore, the indirect action of the anterior pituitary hormone and the direct ac-

tion of estrogens are the etiologic factors. Mammary enlargement of the male is usually self-limited and benign. A period of observation should elapse to determine whether the condition will regress spontaneously. Once established, it does not respond to endocrine therapy. Excision is indicated for cosmetic reasons.

SUBINVOLUTION AND HYPERPLASIA OF THE MAMMARY GLAND

The term chronic cystic mastitis is loosely applied to a group of benign conditions of the breast. Painful breasts and nodular hyperplasia (so-called adenosis or Schimmelbusch's disease) are included under this term. A separate group of cases occurring toward the menopause,

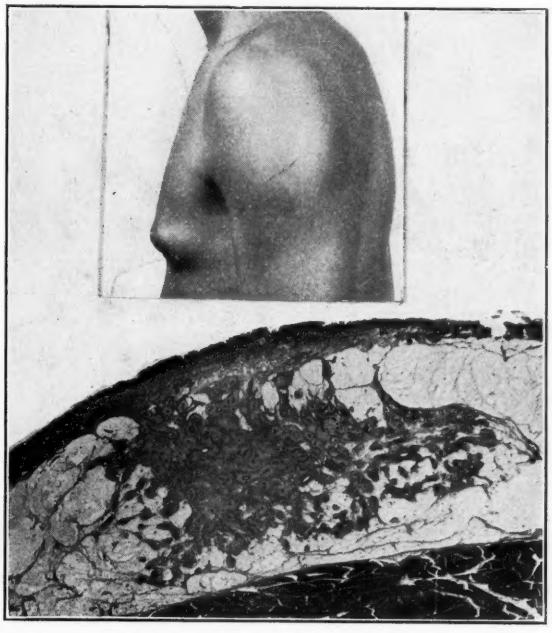

Fig. 3.—Photograph of patient and cross section of the breast, in a case of gynecomastia occurring in a boy aged 18 years.

characterized by cysts of appreciable size and related to abnormal involution of the mammary gland, is also included. With the approach of the menopause or following abnormally high and prolonged estrogenic stimulation, involutional changes occur in the mammary ducts. The epithelial ramifications of the terminal tubules, which form the mammary lobules so characteristic of the normal breast in the childbearing period, atrophy and disappear. The ends of the remaining branches of the ducts dilate and their lining cells secrete. In this phase of involution simple cysts may occur.

Cystic Disease.—Cystic disease is characterized by the development within the breast of one or more cysts of appreciable size. Several cysts may develop over a period of several years in the same patient,

but usually when the patient is first examined there is but one cyst. Cystic disease occurs more frequently in women who have not borne children. In the present series of 580 cases, the cysts, in 80 per cent of the cases, occurred in the forties, or near the menopause. The women affected had regular menstrual cycles and were apparently healthy in other respects. Premenstrual pain or indurated areas in the breast are unusual. Cysts make their appearance abruptly. The known duration

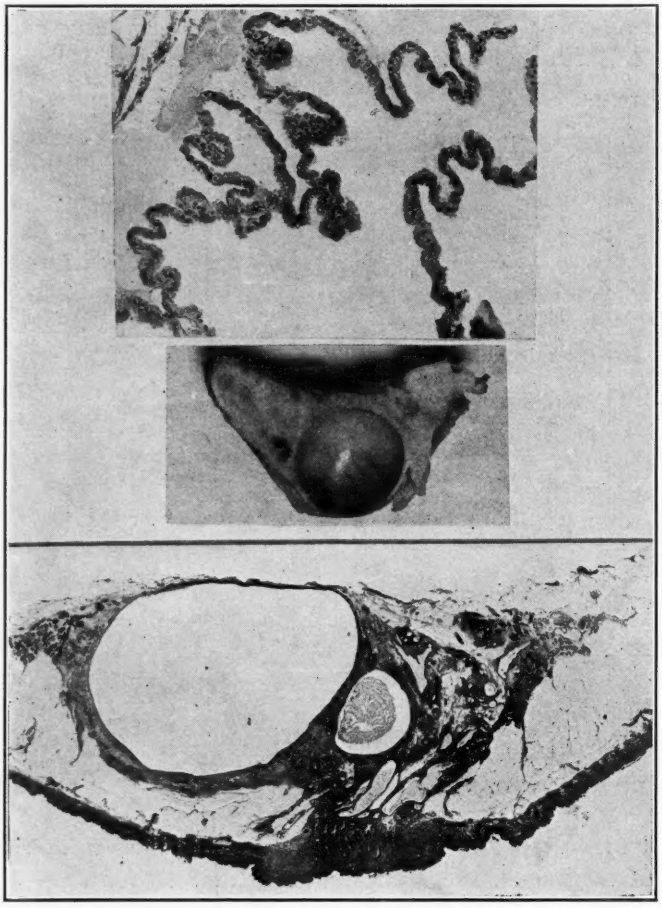

Fig. 4.—Cross section of the breast, gross specimen, and photomicrograph of epithelial lining in cystic disease.

of the tumor is often given in days or weeks rather than in months or years. The breasts affected are well developed and contain increased amounts of fatty or fibrous tissue. The cyst is round, smooth, and freely movable. It transilluminates clearly and upon aspiration cloudy milk-like fluid is obtained. (Fig. 4.) When one or more cysts have appeared and spontaneously disappeared, a residual area of fibrosis may remain. Successive cysts involved both breasts in 17 per cent of the cases. Rarely,

as described by Reclus, multiple cysts of appreciable size may be present at the same time in both breasts. A form of cyst resembling a galactocele may form in a pre-existing fibroadenoma during lactation.

The diagnosis of a cyst may be confirmed by aspiration of the cloudy milk-like contents, and this often suffices for treatment. Following aspiration, injections of estrin (10,000 international units) twice weekly for two months will control the condition in some cases (Lewis and Geschickter). The injections should be halved in number the following month and further decreased in the next month. If there is any doubt concerning the diagnosis, excision should be performed. Cysts with bloody contents or with papilloma in their walls may contain cancer.

Mammary Hyperplasia—Painful Breasts.—A frequent precursor of the lesion that may develop into the hyperplastic form of cystic mastitis or adenosis is the painful breast. This condition is characterized by cyclic pain, which reaches its maximum intensity before the menstrual period. Three hundred and seventy-five cases have been studied. In the early stages the painful and tender tissue is usually in the upper and outer quadrants and feels like a flat, granular area of increased density. Menstruation is usually regular; the patient is in her thirties and either is childless or has not been pregnant for five or more years. In married women with this complaint there is a high percentage of sterility. Mammary pain and tenderness, which are premenstrual in the early stages, become more severe and are prolonged throughout the entire cycle. Fear of cancer is often aroused. An area of increased density may be palpated in the breast. These patients are usually not undernourished and are not of the nervous type. The granular or nodular areas of increased density, which at first vary at different periods of the menstrual cycle, may persist. Spontaneous regression may occur, but often adenosis and less frequently cystic disease supervene after a period of months or years.

This early stage of chronic cystic mastitis characterized by persistent painful breasts may be successfully treated by endocrine therapy (usually estrogen administered intramuscularly twice a week in doses of 10,000 international units over a period of several months as described above for cystic disease). The indurated tender mammary tissue palpated in the outer upper quadrant usually of both breasts in these cases is readily distinguished from the well-defined hard nodule of carcinoma.

Adenosis, Schimmelbusch's Disease, or the Proliferating Form of Chronic Cystic Mastitis.—In married women who have not borne children for five or more years or in childless or unmarried women, painful, shotty masses may develop in the outer, upper quadrants of one or both breasts after the age of 35 years. Many of these women have suffered with painful breasts during the premenstruum for a number of years. As the condition progresses, the stroma of the breast is increased in density and the size of the breast is reduced. The breast

has a saucer-like or liver-like edge. Pain, flat areas of increased density and numerous indefinite nodules are present, but in addition discrete multiple tumors may be palpated, which histologically may prove to be small papillomas, minute cysts, or nonencapsulated adenomatous areas. (Fig. 5.) The 175 patients with typical adenosis in the present study were in the late thirties or early forties with few exceptions. Menstruation is apt to be painful or irregular or the cycle shortened to

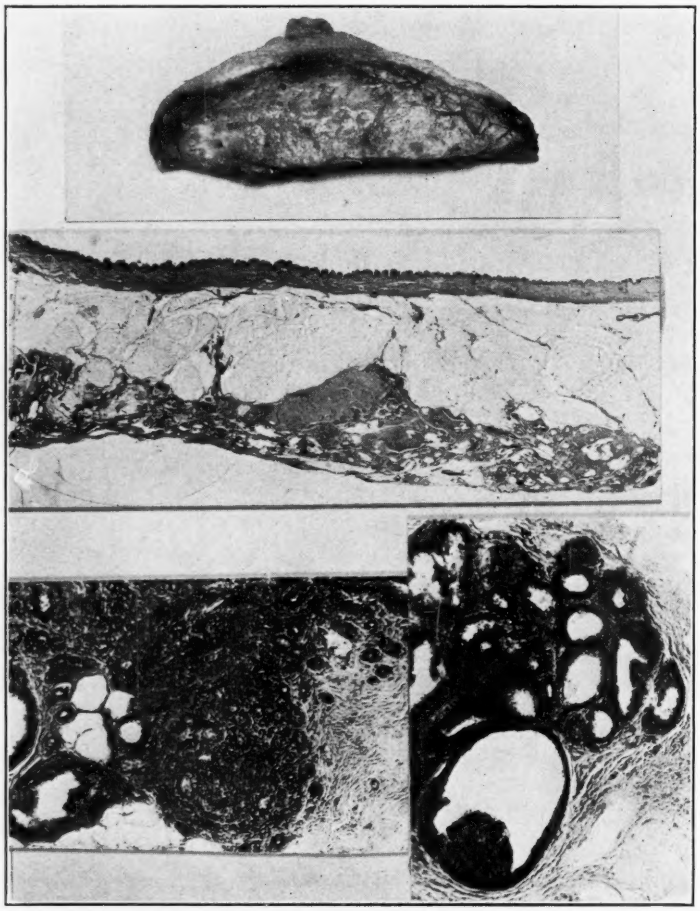

Fig. 5.—Gross specimen, cross section, and photomicrographs in adenosis or Schimmelbusch's disease. The hyperplastic tissue contains small cysts, minute intracystic papillomas, and nonencapsulated epithelial proliferation.

twenty-six days or less. Pregnancy or the menopause may cause these changes to disappear. In rare instances a benign papilloma or a comedo carcinoma develops. Usually, however, the condition is self-limited and terminates with the formation of multiple small cysts. Spontaneous return of the breast to normal before the menopause is rare, occurring in less than 5 per cent of our series. The patients are usually highstrung, nervous, and underweight. The thyroid gland is often moderately enlarged.

Since the condition is bilateral and diffuse, local excision is inadequate therapy. Such excision, however, for purposes of biopsy may be performed where a single nodule, more definite and larger than the others, develops. In our opinion mastectomy is not indicated. These cases show marked improvement on estrogenic therapy beginning with doses of 10,000 international units twice weekly for two months and gradually decreasing by half the number of doses in the succeeding months. Fibrosis or the formation of small cysts may result from such treatment. Many authors believe that this condition is precancerous. In the present series of 533 cases we were able to follow 271 patients for over five years. In only 3 of these carcinoma of the breast developed, an incidence of less than 2 per cent.

Experimental evidence indicates that cystic disease and mammary hyperplasia or adenosis are the result of disturbances in the hormonal physiology of the breast. Large cysts of the mammary gland can be produced in the rat breast by brief, intense stimulation with estrin. In such experiments abnormal epithelial buds replace normal lobule development in the terminal tubules, following injections of large doses of estrin. With further dosage these epithelial masses in the terminal tubules undergo maturation and secretory activity leading to cyst formation. If, instead of estrin, hormones are injected which normally produce lobule development in the rat breast (testosterone), atypical epithelial proliferation with small cysts occurs in the terminal tubules, producing a histologic picture similar to that seen in adenosis.

BENIGN TUMORS

Benign Papilloma.—Hyperplastic epithelium in adenosis is accompanied by the formation of multiple small intracystic masses of basal cells which occasionally take the form of minute papillomas. These rarely exceed the size of a fraction of a millimeter. They tend to regress spontaneously with the menopause. The clinical condition spoken of as intracystic papilloma refers to a tumor of macroscopic size, usually 2 or more cm. in diameter which occurs usually in the region of the nipple or midzone of the breast in women near the menopause. (Fig. 6.) Approximately 50 per cent of these lesions are accompanied by a bloody discharge from the nipple. The tumor is usually palpated near the nipple zone, is soft, or smooth and tense, and is freely movable. It may occur in the ampullae of the nipple itself. The tumor casts a dark shadow upon transillumination.

In 160 benign intracystic papillomas in the present study, the majority had been noted by the patient for two years or more prior to examination. The average diameter of these growths was 3.1 cm. The majority of the cases were 1 to 2 cm. but among cases observed in earlier years 35 were 6 cm. or over. Ninety-five per cent of the tumors were beneath the nipple or in the midzone. Although the peak of age incidence was between 40 and 45 years, the youngest of the patients affected was 15 and the eldest 74. Tumor and serous or sanguineous discharge from the

nipple were the leading symptoms. Variation in size of the tumor following rupture of the cyst and bleeding from the nipple was noted in 6 cases. The tumor on palpation was soft, cystic, or firmly nodular, according to the notes in the history. The nipple was either normal, slightly retracted, or protruded on examination. Fixation did not occur except in the 2 instances where infection had complicated the growth.

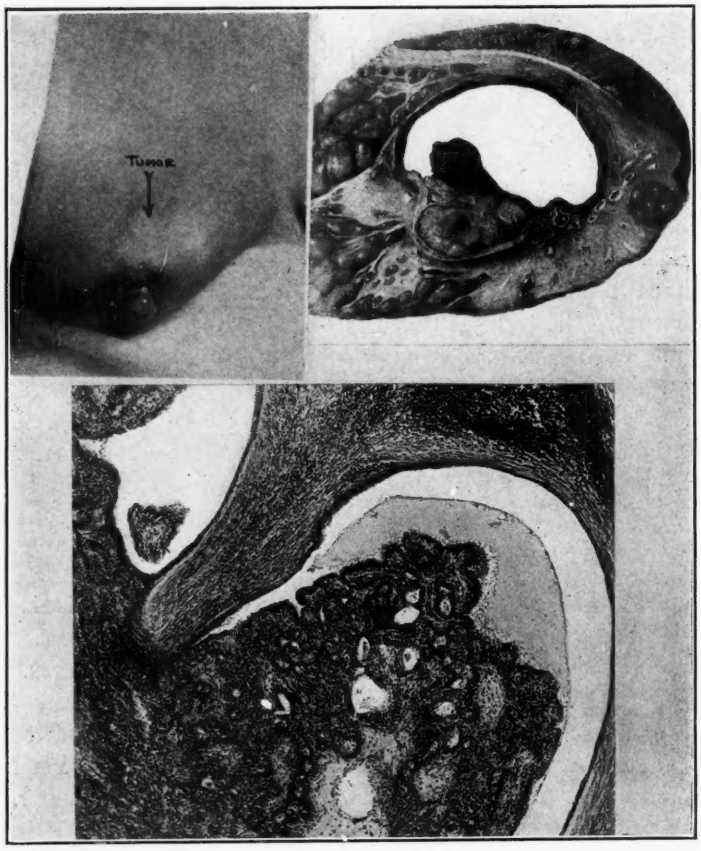

Fig. 6.—Photograph of the patient, the gross specimen, and photomicrograph of benign intracystic papilloma. The tumor is near the nipple and in the gross and under the microscope is completely encapsulated.

On pathologic examination a cyst containing bloody fluid and a soft papillomatous mass are found. In 38 per cent of the cases multiple papillary growths were found pathologically and in 15 per cent of the cases a sanguineous discharge or similar tumor was noted clinically in the opposite breast, either at first or subsequent examination.

Microscopically the tumor consisted of branched stalks of fibrous tissue, overlaid by orderly rows of columnar or oval epithelium. Despite the fact that pathologic study indicates that a certain percentage of these tumors undergo malignant change, simple excision usually suffices to cure.

Forty patients in the present series were treated by the radical operation for cancer. Thirty-eight patients had a simple mastectomy performed, 4 of these having both breasts removed. One had, in addition, excision of a similar tumor from the opposite breast. In all, 82 breasts were amputated for benign intracystic papilloma, 40 of these receiving, in addition, axillary dissection. Up until 1925 only 22 cases were treated by simple excision. This number has been increased to 65 at the time of the present writing. Of these, 6 had two or three excisions.

In this series the radical or simple amputation of the breast was performed for two reasons: First, because the gross or microscopic appearance of the tumor suggested malignancy. In the majority of cases when the radical operation for cancer was performed in the older cases, it was based upon the finding of bloody contents in a cystic tumor at exploration, a finding which was formerly held to indicate the presence of cancer. Second, it was performed because of the opinion formerly held in this clinic and still maintained by many surgeons and pathologists that a sufficient number of these tumors undergo malignant change to justify radical treatment in all cases. This rule is also applied by some in patients having a sanguineous discharge from the nipple without a demonstrable tumor. Twelve of the patients in this series were treated with wide excision of the nipple and breast tissue or by amputation of the breast because of a bloody discharge from the nipple, although no tumor could be demonstrated on examination prior to operation.

A sufficient number of cases treated by simple excision have now been followed to justify the conclusion that benign intracystic papilloma can be treated safely by simple excision. The excised tumor should be subjected to microscopic examination and, if the epithelial contents of the cyst show no evidence of malignancy, no further treatment is indicated. Invasion of the neighboring ducts outside of the capsule of the tumor by epithelium similar to that found in the tumor but without definite papillary formation is the earliest sign of malignant change in our experience. The radical operation should be performed in such cases.

Fibroadenomas.—Fibroadenomas are benign, well-encapsulated tumors, found most commonly following puberty. In 600 cases studied, the peak of age incidence was between 20 and 25 years. The tumors grow slowly, the duration averaging from 3 to 4 years.

In fibroadenomas there is an increase in duct epithelium, periductal and perilobular connective tissue. In many instances no acinar formation is noted, as in virginal hypertrophy and gynecomastia.

Solitary fibroadenomas are most frequently noted in the upper and outer quadrant of the breast at the periphery. On palpation they have a lobulated, elastic feeling and are freely movable. In one-third of the cases the nodule is painful or tender. Rarely does the nodule increase in size during menstruation. Increase in size, however, is the

rule during pregnancy. The breast containing the fibroadenoma or fibroadenomas is usually well developed (Fig. 7). Local excision suffices to cure in these cases, but in about 10 per cent of the cases in which local removal has been performed similar growths have developed subsequently.

Women near the menopause who are treated for this type of tumor usually give a long history when carefully questioned, and at this time

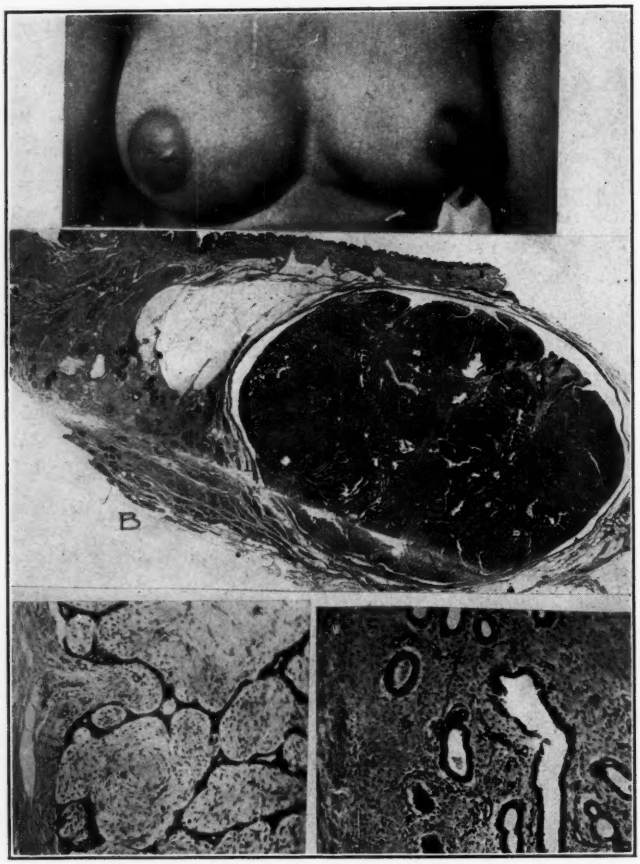

Fig. 7.—Photograph of the patient, cross section of the breast, and photomicrograph in a case of fibroadenoma. The encapsulated character of the tumor is well shown. The photomicrograph on the left shows a myxomatous portion of the tumor; that on the right is typical fibroadenoma.

of life renewed growth energy in the tumor may be noted. In such cases the tumor not infrequently has the histologic appearance of an intracanalicular myxoma, with large amounts of loose embryonic connective tissue surrounding the epithelial structures. In the quiescent cases of long duration a more adult stroma is found. The difference in type of the connective tissue is related to the rapidity of growth and is usually the only distinguishing feature between fibroadenomas and so-called intracanalicular myxomas. In fibroadenomas of long

standing, dilated ducts and small cysts occur. These are sometimes referred to as cystic adenomas. In general, rapid growth of fibroadenomas is incompatible with regular menstruation. Growth of the tumor is therefore most frequently encountered at puberty, in pregnancy, or with the menopause. With repeated menstruation or lactation, the tumor tends to undergo cystic and regressive changes.

Fibrosarcoma.—Rapidly growing intracanalicular myxomas in women beyond the childbearing period are often considered malignant be-

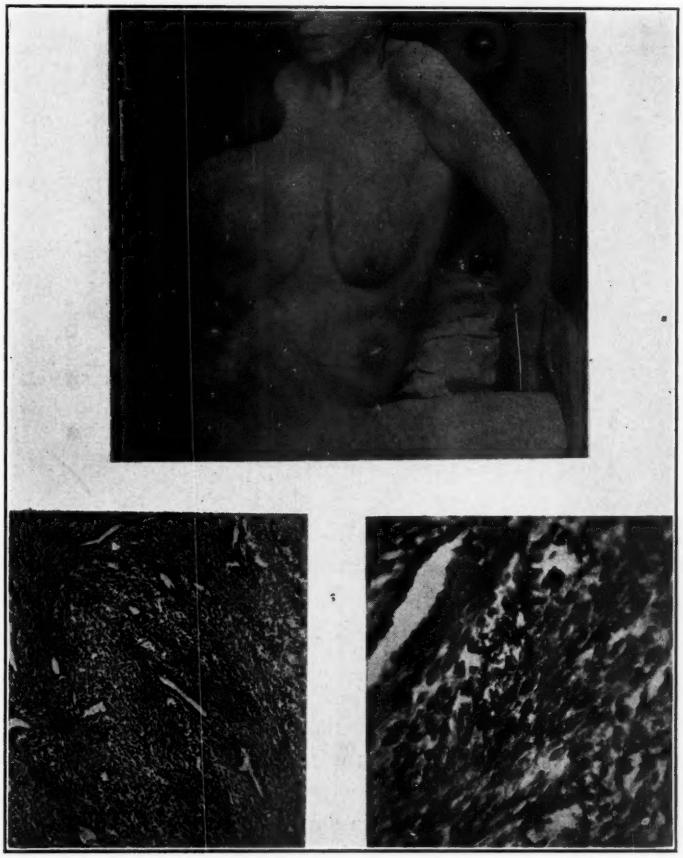

Fig. 8.—Photograph of the patient and low and high power photomicrographs in a case of fibrosarcoma. Many of these cases are rapidly growing fibroadenomas but a few metastasize.

cause of their size, hardness, and nodularity. The majority of the lesions retain their benign character. Fibrosarcoma, however, usually of low malignancy, with invasion of the pectoral muscle but not the axillary nodes, may supervene (Fig. 8). Most of these can be related to preexisting fibroadenomas on the basis of the clinical and microscopic findings. There were 49 such cases in the present series. Usually the malignant tumor develops at the site of a fibroadenoma of many years' duration, the period of rapid growth extending over 3 to 5 years.

Microscopically all gradations can be found from markedly cellular stroma without sarcomatous features, to rapidly growing sarcoma of the spindle-cell type. Because of the tendency for these sarcomas to invade the underlying musculature rather than to metastasize by the lymphatics, an amputation of the breast with the pectoral muscles, but without an axillary dissection, should be performed. In cases treated by simple excision recurrence may result. Nine of the cases of fibrosarcoma in the group of 49 cases studied died of metastases.

CANCER OF THE BREAST

Mammary carcinoma ranks third in cancer mortality tables, being exceeded only by cancer of the stomach and uterus. The present-day curability of all forms of mammary cancer by radical surgery is variably stated, the figures usually ranging between 30 and 40 per cent. Attempts have been made to increase the number of cures in three ways: by education of the public and profession to secure earlier diagnosis and treatment; by combining irradiation and surgery; and by preventive measures directed against certain allerged precancerous lesions of the breast.

An analysis of 2,300 cases of cancer of the breast treated over a period of fifty years (1889 to 1938) at the Surgical Clinic of the Johns Hopkins Hospital shows that the curability of breast cancer varies with the pathologic type as well as with the stage of the disease. It indicates a 5 per cent increase in the curability of all forms of mammary cancer in the last two decades as a result of the educational campaign.

Infiltrating Adenocarcinoma or Scirrhous Mammary Cancer.—Approximately three-fourths of all mammary carcinomas arise from the glandular epithelium of the terminal tubules. This common variety of adenocarcinoma, variously termed gland cell or scirrhous cancer, is seen clinically in four different forms.

It occurs usually as a tumor, 1 to 5 cm. in diameter with atrophy of the overlying fat and with or without retraction of the skin or nipple. It may occur as a large mass occupying one or more quadrants of the breast. In other cases one or more recurrent nodules are found in the scar of a preceding operation. In a small group of patients a relatively small tumor with extensive skin involvement, so-called acute or inflammatory cancer, is found. (Fig. 9.)

The usual form of scirrhous cancer is a small hard mass, 1 to 3 cm. in diameter occurring at or near the menopause in a woman who has

CLINICAL TYPES OF INFILTRATING (SCIRRHOUS) CARCINOMA OF THE BREAST

TYPE	CHARACTER OF TUMOR	NO. OF CASES	FIVE-YEAR SURVIVALS
1. Small infiltrating cancer	1 to 5 cm. in size	1050	29%
2. Large infiltrating cancer	6 to 14 cm. in size	420	5%
3. Recurrent cancer	One or several nodules	220	7%
4. Acute or inflammatory cancer	Extensive skin involvement	20	0%

borne one or more children. The majority of the cases occur between the ages of 40 and 55 years. The patients have noticed the presence of a lump or nodule six months or less prior to the time of examination.

The clinical history and findings in the ordinary form of small infiltrating mammary carcinoma under discussion are remarkably uniform. The four major findings on the examination of the breasts are: first, the presence of a single lump in a breast otherwise normal to palpation; second, the hardness and irregularity of the tumor to palpation; third, the apparent nearness of the tumor to the examining finger be-

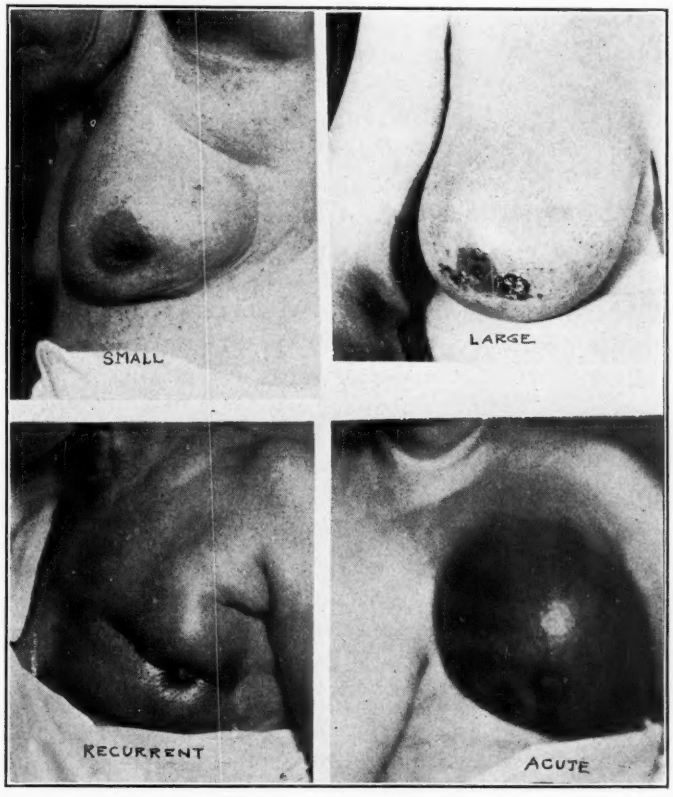

Fig. 9.—Photographs of patients with small, large, recurrent, and acute forms of infiltrating adenocarcinoma (scirrhous cancer).

cause of atrophy of the overlying fat; and fourth, retraction of the skin or nipple indicated in their earliest phases by dimpling of the skin or a difference in the position of the nipple on the affected side when the patient in the erect position slowly elevates her arms. Discharge from the nipple is not a common symptom in this group and was noted only 26 times in the series of 1,050 cases.

Pathologic findings are as uniform as those observed clinically. The tumor on section is usually a dense whitish yellow stellate mass which is gritty and its surface retracts or "cups" when cut through with a knife.

Small secondary masses may be found in the neighborhood of the main growth or the tumor may be elongated and may extend toward the nipple or toward the periphery of one of the quadrants of the breast. The surrounding breast is usually fatty with traversing bands of fibrous tissue and poor in parenchymatous tissue. The tumor most frequently is found in the outer and upper quadrants or in the upper inner quadrants of the breast, but it may occur in any of the various quadrants or in the central zone.

On microscopic examination the tumor cells are of moderate size with moderate amounts of cytoplasm with vesicular nuclei which contain distinct nucleoli and occasional mitotic figures. The cells grow characteristically in small nests or islands or narrow elongated cords with large amounts of intervening fibrous tissue and small amounts of lymphoid infiltration. In the more slowly growing tumors the cancer cells are dispersed by large amounts of fibrous tissue or form acinar or tubular structures. (Fig. 10.)

Although the more unfavorable cases of scirrhous carcinoma, including those exceeding 5 cm. in diameter, recurrences following incomplete removal, and acute carcinoma, have been excluded from the group of small infiltrating scirrhous cancer, the results following radical surgery show that only 30 per cent of the patients survived the five-year period. These results are in keeping with those of Hutchinson who collected figures from fifty clinics and found the surgical results showed 28.1 per cent of five-year survivals.

While this group of small infiltrating cancers represents only one-half of the entire series of mammary cancers, the percentage of five-year cures is fairly representative of the entire group. This is true because the remaining half is about equally divided between large advanced or hopeless cancers in which the percentage of cures is 7 per cent and low grade cancers including carcinoma secondary to benign papilloma, to chronic cystic mastitis and gelatinous carcinoma in which the cures average 61 per cent.

Large Infiltrating Scirrhous Carcinoma.—In 420 cases in the present series the tumor measured 5.5 cm. or more in diameter. These cases were similar in other respects and belonged microscopically to the same group as small infiltrating scirrhous carcinoma. This group of cancers is characterized by a diameter greater than 5 cm., by their hard nodular character on palpation, and by their adherence to the overlying skin, with or without ulceration. They have been grouped separately because of their extremely unfavorable prognosis. With but four exceptions, metastasis to the axillary glands had occurred prior to treatment and only 8 cases survived the five-year period. A study of this group demonstrates that a scirrhous cancer (recognized on palpation by its hard and fixed character) which has reached a size of more than 5 cm. in its greatest diameter is incurable by radical surgery. Irradiation or some other form of palliative therapy (simple mastectomy) is indicated.

Except for their longer duration and a younger average age, the symptoms of large infiltrating scirrhous carcinoma resemble those found in smaller tumors of the same type. A higher percentage noted pain or tenderness prior to examination and had not sought treatment previously because the lump had not caused pain or discomfort. One-fourth of

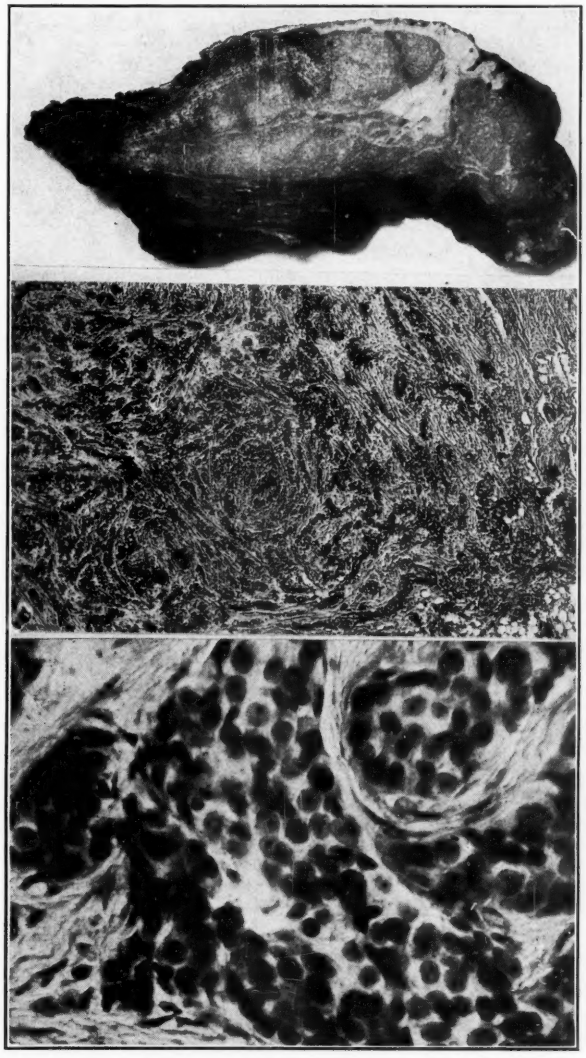

Fig. 10.—Gross specimen, and low and high power photomicrographs of infiltrating (scirrhous) adenocarcinoma.

the cases had noted that the overlying skin had become "angry" or ulcerated and mentioned this as a reason for seeking treatment. (Fig. 11.)

This group of cases presented all the classical signs of cancer of the breast emphasized in the older literature. The tumors occupied one or

more quadrants of the breast. They were hard and fixed to the overlying skin and sometimes to the underlying muscles. Discoloration, edema with "orange peel appearance" secondary nodules in the skin, ulceration, and fungating tumors were among the skin changes noted. Enlarged axillary nodes were noted with few exceptions in the histories and microscopically they contained metastases in all but 4 cases. Discharge from the nipple was noted in 3 per cent of the cases and was described as bloody, foul, or pus. To this group belongs the greatest number of cancers which ultimately involved both breasts. In 12 of the pa-

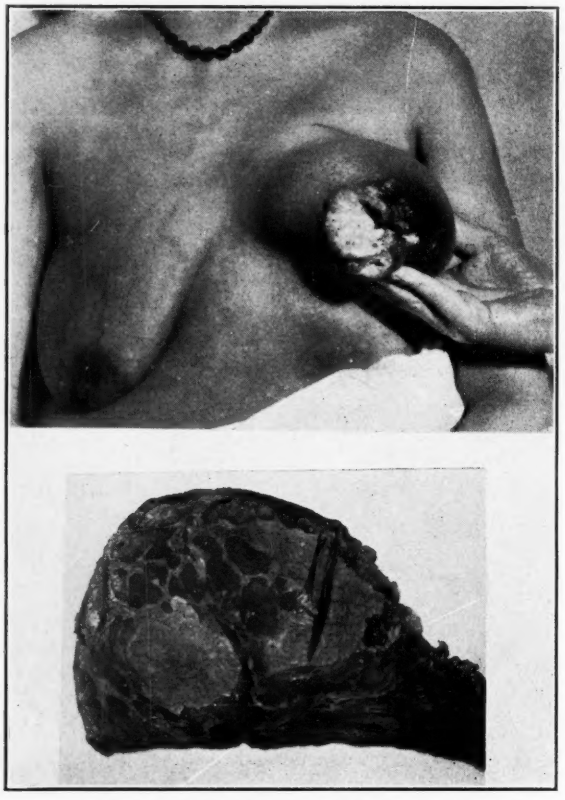

Fig. 11.—Photomicrograph of patient and gross specimen illustrating an advanced case of large infiltrating scirrhous cancer.

tients both breasts were apparently involved at the time of first admission, the bilateral amputation being done in 2 on the first admission and in the remaining 10 with an interval of about one month between the removal of right and left breasts.

These cases are remarkable pathologically for the absence of necrosis and softening in the tumor in spite of its size. In a few instances secondary infection entering via the pathway of the nipple and larger ducts caused areas of degeneration and necrosis. In many instances the tumor was infiltrated throughout the mammary tissue. In other cases

two or more large masses with adjoining surfaces or connected by infiltrating strands of tumor were found on section. Microscopically these large tumors do not differ from the smaller scirrhous cancers.

All of the cases in the present series of large infiltrating scirrhous cancers were treated surgically, although some of the recent cases had pre- or postoperative irradiation. In the earlier decades many received radical Halsted operations, though in some instances the supraclavicular and axillary regions were dissected after an interval of days or weeks following the amputation of the breasts with the pectoral muscles. In the more recent cases the larger tumors with ulceration or skin involvement were treated by simple amputation of the breast including the pectoral muscle in combination with irradiation with no attempt to perform the axillary dissection. Although this group of cases is inoperable according to modern standards, 8 cases survived the five-year period.

Recurrent Cancer.—In 220 cases of mammary cancer in the present series radical operation was performed for recurrence after incomplete operation or dissections were performed for recurrent masses following a previous complete operation for cancer. In this group of cases there are many who had repeated operations for recurrences. One patient had a complete operation in December, 1921, and had twenty local operations for recurrences, finally dying in July, 1928, supposedly from pneumonia. In a similar case the tumor was first excised in 1926, the radical operation was done in 1929, and two local operations done for recurrence in 1930, the patient ultimately dying in 1933. Usually the local recurrence appeared within 1 to 2 years following the complete operation, or sooner if an incomplete operation was performed. There are 14 cases, however, in which the local recurrence took place 5 or more years after the complete operation. In one case the first recurrence was 20 years after the complete operation, in one case 12 years after, and in three cases, ten years after the complete operation. In all there were 28 cases in which both breasts were ultimately involved. With the exception of 4 cases, these patients did not survive the five-year period, following the appearance of the recurrence.

In a small group of cases known as acute or inflammatory carcinoma skin metastases appear before a nodule of appreciable size is discovered in the breast. Fortunately this type of carcinoma with early skin manifestations (sometimes spoken of as erysipeloid cancer) is rare and occurs only 20 times in the present series. There were no five-year survivals in this group, although palliative results were obtained with deep x-ray therapy.

CIRCUMSCRIBED FORMS OF MAMMARY CANCER

One-fifth of the cases of mammary carcinoma in the present series differed clinically and on gross examination from the more common variety of scirrhous cancer. Microscopically, this smaller group includes

carcinoma secondary to benign papilloma, gelatinous or mucoid cancers, and comedo carcinoma growing in the mammary ducts. They are characterized by a slower growth and a better prognosis (there are 61 per cent of five-year survivals). Clinically these tumors are distinguished by their softness on palpation and by their circumscribed form.

CIRCUMSCRIBED FORMS OF MAMMARY CANCER

TYPE	CHARACTER	NUMBER	FIVE-YEAR SURVIVALS
Papillary adenocarcinoma	5 to 6 cm., soft, circumscribed	260	60%
Gelatinous cancer	4½ cm., long duration, cystic	75	58%
Comedo carcinoma	localized or diffuse	135	67%

Papillary Cancer.—The majority of the circumscribed forms of mammary cancer show a papillary structure, both in the gross and under the microscope (Fig. 12.) They are often of large size and of more than a year's duration. The central portion of the breast near or beneath the nipple was affected in one-sixth of the cases in this series and a sanguineous discharge from the nipple occurred in 10 per cent. The growth differs from scirrhous cancer, being softer to palpation and remaining in many instances freely movable despite its size. Distant metastases occur late and local recurrence or involvement of the other breast often precedes metastases to the internal organs. Thirty per cent of these cases occurred in the colored race; whereas, in other forms of cancer slightly over 20 per cent were affected.

In the present series there were 260 cases of papillary carcinoma. The average size of these tumors is between 5 and 6 cm. Some were about one-half this size, but not a few involved the entire breast. A little less than 50 per cent of the cases gave a duration in terms of years rather than months, and of this group the duration of 3 or more years was not uncommon. There is a wide age distribution in this group, practically equal numbers occurring in each decade between 30 and 70 years. The occurrence of a sanguineous discharge from the nipple, a location near the center of the breast, and the microscopic appearance justify the conclusion that many of these cases of papillary cancer are late manifestations in a pre-existing benign papilloma.

The tumor in the gross is hemorrhagic, necrotic, or cystic. The cut surface is friable and stringy. The tumor masses are well circumscribed at the periphery, often with a necrotic or cystic center.

Under the microscope the characteristic feature is the persistence of the fibrous stalk supporting loops or folds of glandular cells of varying shapes and sizes. The predominant epithelial cell is malignant in character with a large vesicular nucleus and a moderate amount of cytoplasm. Many of the cells, however, are small and oval in appearance, surrounding a small central lumen to form acinar structures.

In some cases multiple benign papillomas are found in the region of malignant growth upon microscopic examination. In 12 cases multiple tumors in one or both breasts were found in the clinical examination. Microscopically a benign papillary structure is sometimes seen with malignant change at one margin and in 6 cases mucoid degeneration was found in the malignant papilloma. In 12 cases both breasts ultimately were involved.

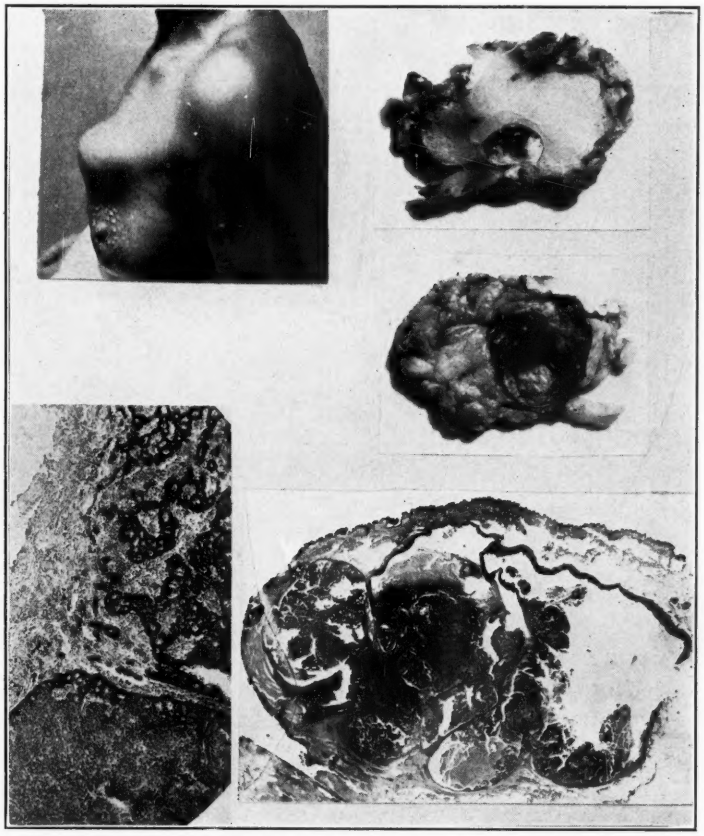

Fig. 12.—Photographs of the patient and the gross specimen and photomicrographs of papillary adenocarcinoma. These tumors are usually sharply circumscribed as shown in the illustrations.

Papillary adenocarcinoma may be cured by radical operation even in advanced cases. Among the five-year survivals, tumors of 5 cm. or larger are nearly as common as those of small size. In 8 cases surviving the five-year period, the tumor was 10 cm. or over in size. In 1 patient who was 69 years of age at the time of examination, a tumor of 14 cm. of 3 years' duration was found. There was a local recurrence 4 years after the radical operation, which was treated by excision, and the patient died of other causes 17 years after the primary operation. A patient with a tumor of similar size died of cancer 17 years after a radical

operation in which the dissection was carried out above the clavicle because of metastases to the glands of the neck. In other cases in which the patient died of the disease, late local recurrence is a striking feature. The recurrence in some instances appeared from 5 to 16 years after the radical amputation. Because of the large size of the tumor, there is a tendency to sacrifice only the skin overlying the mass with very little additional margin. This accounts for the high percentage of local re-

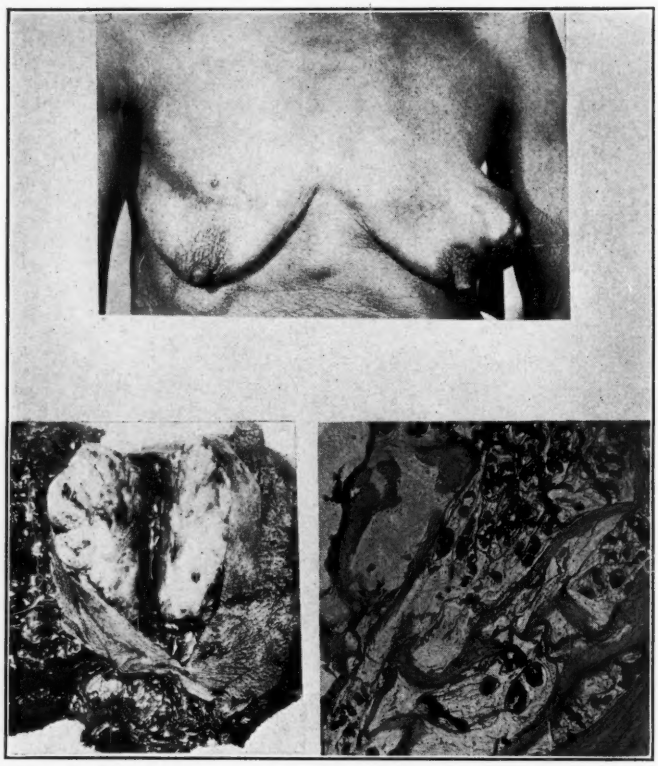

Fig. 13.—Photograph of the patient, gross specimen, and photomicrograph from a case of gelatinous carcinoma. In the photograph of the patient note the enlargement and protrusion of the nipple on the affected side.

currences observed in these cases. Despite the size of the growth and the local recurrences, 60 per cent of the cases survived the five-year period.

GELATINOUS, COLLOID, OR MUCOID CANCER

Three per cent of breast carcinoma shows a gelatinous or mucoid intercellular substance in the gross and under the microscope (Fig. 13). The gelatinous character of the tumor has been variously ascribed to degeneration of connective tissue stroma or a secretory product of the epithelial cells. Lang was the first to emphasize the slow growth and relatively benign course of these tumors. Lee, Hauser, and Pack studied

30 cases of mucoid cancer and found the five-year survivals to be 57 per cent as compared to 41 per cent in a control group.

Like papillary carcinoma, mucoid cancer is a slowly growing and low grade form in which arrestment of the disease may be achieved by surgery in advanced cases. Gelatinous carcinoma also resembles papillary cancer in its tendency to occur beneath the nipple (15 out of 75 cases) and to be accompanied by a sanguineous discharge (10 cases). Other similar features are a duration of symptoms of years rather than months, an even age distribution in the decades between 30 and 70 years, an encapsulated and circumscribed character in the gross, which often leads to the clinical impression of a benign lesion, and an association under the microscope with benign intracystic papilloma.

The outstanding clinical features of mucoid mammary cancer are the relatively small size of the tumor in comparison with the long duration of symptoms, the peculiar fluctuant or "swishy" consistency of the tumor suggesting a ruptured cyst, the occurrence of bulging of the nipple rather than retraction when the tumor is in the nipple zone, and the freely movable character of the growth. The average size of tumor in this series was 4.5 cm. and approximately 50 per cent had a diameter of 3 cm. or less. Nearly one-half of the cases had a duration in terms of years rather than months. Nine patients were aware of the tumor for 6 years or longer; 1 had noted the tumor for 48 years, dying with metastases 5 years after operation. A patient who had noted the tumor in the breast 24 years before operation was living and well 15 years after the treatment, and another who had a tumor 8 years died 6 years after a radical mastectomy.

Because of the gelatinous and fluidlike consistency of the tumor and the absence of fixation, the initial clinical interpretation was that of a benign cyst in 11 cases. The occurrence of multiple nodules led to an interpretation of a benign tumor in other instances. Four cases were first diagnosed fibroadenoma; and two, papilloma. In all, 19 cases were initially treated by excision. With few exceptions this was followed by the complete operation within a few days. The differentiation from benign cysts should not be difficult since these cancers are near the skin surface, are less tense and rounded on palpation, and are often accompanied by discoloration of the overlying skin with atrophy of the intervening fat.

The appearance of gelatinous cancer in the gross is characteristic. Gray translucent lobules resembling tapioca or semifluid mucoid material which flows from the tumor on section are diagnostic. Under the microscope, acini or strands of small epithelial cells are dispersed in large amounts of light staining mucoid substance. The microscopic studies indicate that gelatinous cancer is the result of secretory changes in a slowly growing form of adenocarcinoma. In 8 cases in the present series the origin of cancer could be traced to pre-existing benign papilloma. In 1 patient an excision for benign intracystic papilloma

had been performed 23 years previously and the recurrent tumor at the same site showed, in addition to the characteristic mucoid change, the persistence of a papillary structure. In the majority of cases a papillary structure could not be found and the more solid epithelial portions of the growth suggested a slowly growing adenocarcinoma.

The results of treatment of mucoid cancer are similar to those of papillary cancer in that radical mastectomy accomplishes approximately 60 per cent of five-year cures. In the present series there are 33 cases surviving the five-year period; 27 are known to be dead and 20 are untraced. On the basis of five-year follow-ups (omitting 2 recent deaths), there are 58 yer cent of five-year cures. While radical mastectomy is unquestionably the treatment of choice in these cases, 1 patient is reported well 14 years after simple mastectomy and another is living 15 years after excision of a recurrent tumor and 7 years after the local removal of an axillary lymph node which showed metastasis on microscopic examination. In 2 additional cases where excision only was performed, 1 is still living 4 years later, and another died of metastases at the end of 4 years. Two other cases were treated by simple mastectomy. One died two years later and 1 has not been traced. In the cases where simple excision preceded the complete operation, the local removal apparently did not interfere with the percentage of cures established by radical operation.

Although slightly less than 60 per cent survived the complete operation more than five years, there are many cases in this group of survivors that ultimately die of the disease. One patient died with mediastinal metastasis and extension to the neck 35 years after the complete operation and another patient who had the tumor 20 years before the complete operation died of metastasis 6 years after. The fluidlike consistency of the tumor predisposes to transplantation and local recurrence and ultimately to metastases.

COMEDO CARCINOMA

The germinal epithelium of the terminal tubules retains the power of growth throughout sexual maturity and is capable of forming additional mammary tubules as well as acini in response to hormonal stimuli during the menstrual cycle or pregnancy. Abnormal hormonal stimuli may result in hyperplasia of these elements, producing minute papillomas and benign adenomas characteristic of the proliferative form of chronic cystic mastitis, or adenosis. Malignant proliferation in these terminal tubules is common after menopause and gives rise to the most prevalent form of mammary cancer, infiltrating scirrhous carcinoma. Our studies have failed to reveal any etiologic connection between the hyperplasia of these germinal buds in adenosis and the malignant proliferation observed in scirrhous carcinoma.

A low grade form of malignancy, however, may arise in the epithelium of the small tubules or from the basal cells beneath the lining of the

larger ducts and for a long time may remain confined by the normal boundaries of the duct tree. This rare form of mammary cancer which may be associated with adenosis has been termed by Bloodgood comedo cancer. The term comedo is applied to such a tumor because, when it is cut, plugs of tumor cells may be expressed from the ducts similar to the plugs or comedones expressed from an ordinary blackhead on pressure. (Fig. 14.)

There were 136 cases of comedo carcinoma in the present series. In one group, the so-called pure comedo cancer of Bloodgood, the tumor cells at the time of operation had not infiltrated beyond the basement

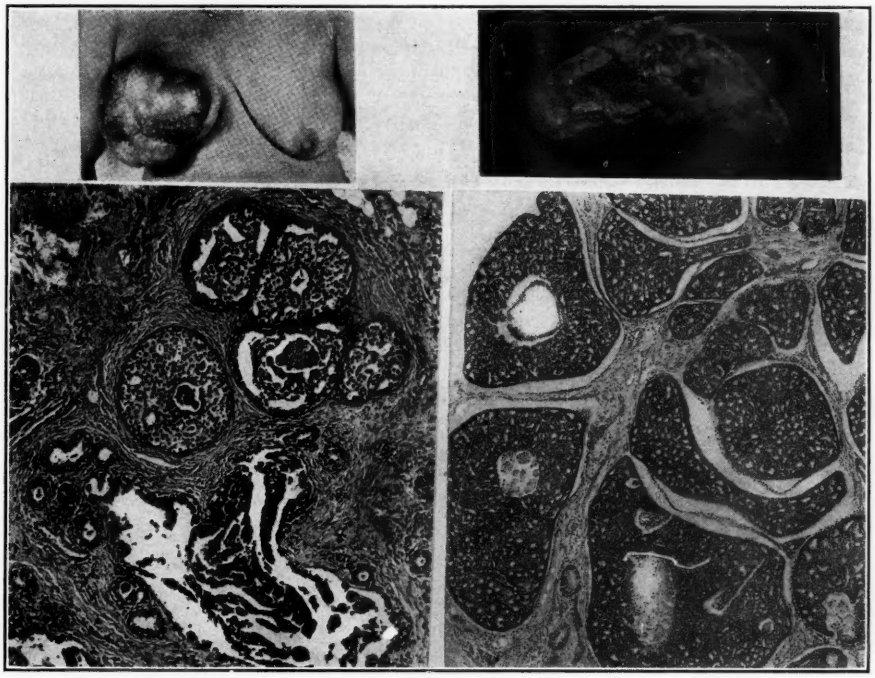

Fig. 14.—Photographs of the patient, the gross specimen, and photomicrograph illustrating the features of comedo carcinoma. The small plugs of tumor tissue can be seen in the gross. The high powered photomicrograph shows the presence of papillary hyperplasia or adenosis in the breast tissue adjacent to the tubules which are infiltrated by cancer.

membrane of the ducts. In the other group of cases, infiltrating comedo carcinoma, the tumor tissue at the time of operation was largely confined within the preformed ducts, but in addition cancer cells infiltrated beyond and invaded fat and fibrous tissue. This group of 135 cancers, which comprises 5 per cent of all forms of mammary cancer, is the only form of malignancy in the present series which showed a tendency to occur in the breast which was the seat of adenosis. Approximately one-third of the cases showed such changes. This form of cancer, moreover, is the most favorable form from the standpoint of treatment and shows 67 per cent of five-year cures.

The cases of "pure" comedo carcinoma in the 52 patients observed in this series present either of two characteristic clinical pictures. In one, a slowly growing tumor involved the greater part of the affected breast and an isolated tumor could not be palpated in the enlargement. Despite the size of the growth, there were frequently no palpable lymph nodes. In the second, clinical type, the tumor was small, measuring from 1 to 3 cm. in diameter. One or more of such freely movable nodules were palpated just beneath the skin. The age of the patients with comedo carcinoma averages 46.7 years. In about 25 per cent the tumor was of over 2 years' duration, and in 6 it had been noted for 5 years or more. The location of the comedo carcinoma suggests an origin in or near larger ducts. It often develops near the nipple at the margin of the areola, in many cases just above and to the outside of the nipple. Symptoms referable to the nipple are common. A watery milky or yellowish discharge is noted not infrequently. Retraction or fixation of the nipple occurs often, and occasionally the patient complains of burning and itching of the nipple, a symptom more common in Paget's disease. In a few cases a serosanguinous discharge from the nipple was noted.

The tumor is usually located near the skin, and atrophy of the overlying fat and dimpling occur. Redness of the skin is sometimes noted. The tumor remains movable. Even when the growth is larger than 6 cm. in diameter, there will be no fixation to the wall of the chest.

When the tumor is sectioned, characteristic plugs of tumor tissue can be expressed from the larger ducts. The growth is usually infiltrating.

Comedo carcinoma arises from small oval cells with dense nuclei and scanty cytoplasm. There are numerous intermediate cell forms which show a differentiation into duct epithelium with an irregular secretory border. These cells, the nuclei of which show no conspicuous malignant features, form a thick lining or wall in the ducts. The larger secretory epithelium surrounds the central lumen of the duct, which contains secretory débris; the smaller basal cells rest on a basement membrane, which sharply demarcates the duct epithelium from the periductal fibrous tissue. All of the duct channels throughout one or more quadrants of the breast may show this characteristic hyperplasia of the lining epithelium. The tumor cells not only line pre-existing ducts but form new secretory channels, so that small secondary openings appear in the cross sections of the lining epithelium of the larger ducts. The tumor grows slowly and metastasizes late, if at all, to axillary lymph nodes. In cases in which metastases occur, the epithelium in the lymph nodes shows the characteristic thick-walled ducts lined by secretory epithelium with numerous transitions toward basal cells.

Of all the forms of carcinoma of the breast, comedo carcinoma offers the most favorable prognosis. There are 85 per cent of five-year cures in this group of cases. The majority of the patients living more than 5 years after operation have remained well for 10 years or more. Three

patients have remained well more than 20 years, and a fourth patient has remained well for 36 years. The duct carcinoma composed of transitional epithelium related to Paget's disease of the nipple does not afford as favorable a prognosis.

Of 35 patients traced, 1 died of metastases after 5 years, and 3 others died of metastases after 4, 3, and 2 years, respectively. The remainder were well after 5 years (85 per cent five-year cures), but 1 of these died after 6 years, a cancer of the opposite breast having developed.

There were 8 cases of comedo carcinoma in which the initial treatment consisted of local excision. In 6 of these the growth recurred locally—in 1 to 4 years. In these cases radical operation was performed later, and metastases to the axillary nodes were found at the second operation. In the 2 additional cases treated by local excision, 1 of the patients, the wife of a physician, has remained well for 11 years, no other operative intervention having been necessary. A second patient is now well, showing no evidence of recurrence after 3½ years. One patient was treated with irradiation followed by amputation of the breast without axillary dissection. This operation was performed in May, 1934, and the last report, made at the time of writing, stated that the patient was dying of metastases to the bone and to the skin over the wall of the chest.

Infiltrating Comedo Carcinoma.—The pure form of comedo carcinoma just discussed grows slowly and remains confined to the ducts over a period of years and metastasizes very late to the axillary nodes. In the group about to be described, there were 84 cases of infiltrating comedo carcinoma which resembled histologically those previously described but which showed, in addition, cancer cells infiltrating beyond the basement membrane of the ducts and invading fat and fibrous tissue. That this group represents a more rapidly growing form of comedo carcinoma rather than late cases of the pure form is indicated by the age distribution which parallels that of pure comedo cancer, by the shorter duration of symptoms, and by the comparatively small size of the tumor. The average age of infiltrating comedo carcinoma was 45 years compared to an average age of 46.7 years in the noninfiltrating or circumscribed form. The average duration of symptoms in the 28 cases of infiltrating comedo cancer which had noted a tumor for more than a year was 3½ years and the average duration for 48 cases who had noted a tumor for less than a year was 3.6 months. The average size for all the tumors in the group was 4.8 cm.

The clinical characteristics of these tumors resemble those of the noninfiltrating form of comedo cancer rather than scirrhous cancer in that they are frequently freely movable and are often associated with the larger ducts near the nipple. In this group there were 6 patients treated by local excision in the first instance. One of the recent cases had no further operation. Three had the complete operation within a month following local excision and 2 of these died within a year, the third not being traced. In the 2 remaining cases the excision preceded the com-

plete operation by more than 1 year. Both, however, have remained well for 14 years following the complete operation.

At the time of writing, 27 cases have not been traced for a period sufficient to learn the results of treatment and 55 have been followed. Twenty-seven of the followed cases are known to be dead, and 28 have survived the five-year period. All the cured cases except the 2 just mentioned were treated by radical surgery. None of the cured cases received preoperative irradiation. There are 51 per cent of five-year survivals.

PAGET'S DISEASE OF THE NIPPLE AND DUCT AND PAGETOID CANCER OF THE BREAST

Since Paget's clinical description in 1874 of cancer of the female nipple and Butlin's microscopic study of the disease in 1876, cancer of the breast characterized by large cells resembling squamous epithelium has been recognized as a separate form. The exact definition or limit of the disease, however, has been much disputed. Clinically there has been a tendency to classify as Paget's disease any lesion of the breast producing destruction of the nipple. However, cancer characterized by large epidermoid-like cells of the Paget type may occur in the breast without involving the nipple. A definite group of carcinoma of the ducts resembling Paget's cancer of the nipple under the microscope may remain confined to the ducts or invade the substance of the mammary gland and not the nipple. Another group of cases of so-called cancer cysts contain epithelium resembling the Paget type but arise within the substance of the gland.

In the 2,300 cases of cancer of the breast in the present series there were 62 cases which had been routinely classified as Paget's cancer. These were characterized by lesions of the nipple and by the presence of typical Paget cells which involved the nipple and with few exceptions the mouths of the adjoining ducts. In 40 of these cases a cancerous mass was also found in the mammary tissue at some distance from the nipple. There was a second group of 25 cases of duct carcinoma in which the tumor was characterized by large "Pagetoid cells," originating in and for the most part confined to the larger ducts. Seven of these were accompanied by a discharge from the nipple but none produced ulceration or histologic invasion of that organ. There was a third group of cancers histologically resembling Paget's disease of the nipple or Pagetoid duct cancer. This group of 74 carcinomas of the breast showed little or no tendency to involve the larger ducts or to invade the nipple. They gave rise to distinct mammary tumors which were usually characterized in the gross as cancer cysts, the enclosed cavity containing blood or necrotic tissue.

These three groups of carcinoma totaling 161 cases apparently arise from a more primitive form of transitional epithelium and have been

selected for special study on the basis of their microscopic appearance. There are two embryonic components from which the breast develops. The more primitive, the milk line, is composed of several layers of thickened epidermis, appearing in the embryo of mammals as bilateral bands connecting the sites of the future nipples. The second embryonic component, mammary bud, appears beneath the milk line. This is a small mound of undifferentiated epithelium derived from the basal cell layers of the epidermis.

In subsequent development the system of primary ducts is formed by the extension of the process of differentiation beginning in the milk line. In the embryo these large milk channels are formed by the hypermaturation of squamous cells which are identical with those found in the epidermis. Ultimately the epidermoid lining of the large mammary ducts is replaced by mammary duct epithelium. However, the persistence of epidermoid cells in the nipple and in the mouths of the larger ducts accounts for the appearance of epidermoid or Paget's cancer in these structures in later life. A persistence or reappearance of the primitive epidermoid lining in the larger mammary ducts some distance from the nipple accounts for a form of duct cancer resembling Paget's disease of the nipple and for epidermoid carcinoma or cancer cysts which may occur deep in the breast tissue.

Paget's Disease of the Nipple.—Paget's cancer is characterized by invasion of the epidermis of the nipple or areola and (usually) the mouths of the larger ducts by malignant cells resembling those seen in transitional cell cancer of the skin or mucous membranes. The malignant cells differ somewhat from the usual epidermoid carcinoma and for this reason have become known as Paget cells. (Fig. 15.) The clinical histories are of two types; one in which nipple symptoms precede a tumor in the breast and the other in which a lump in the breast precedes symptoms referable to the nipple.

Regardless of the mode of onset, all the cases of Paget's cancer included in the present study ultimately involved the nipple. The evidence in the present study indicates that cancer of the Paget type begins either in the larger duct beneath the nipple or in the basal cell layers of the epidermis of the nipple itself, in cells predestined to form mammary ducts. That the tumor may begin in the basal cells of the nipple is indicated first by two benign cases in which keratosis of the nipple only was found, at the time of the first examination, and which returned after an interval of a year or more with ulceration of the nipple showing cancerous changes on excision. Second, a series of 19 cases where malignant Paget cells were found in the nipple, in which either the simple mastectomy or radical mastectomy was performed, and subsequent examination of the amputated breast failed to reveal any evidence of the disease outside of the nipple. Third, a

small group of cases in which Paget cells were found in the nipple and cures were established by local excision.

That Paget's cancer may begin in a duct beneath the nipple is indicated by a group of duct cancers, with Pagetoid cells (to be described subsequently) which do not involve the nipple and by a few cases of this type which showed involvement of the nipple late in the course

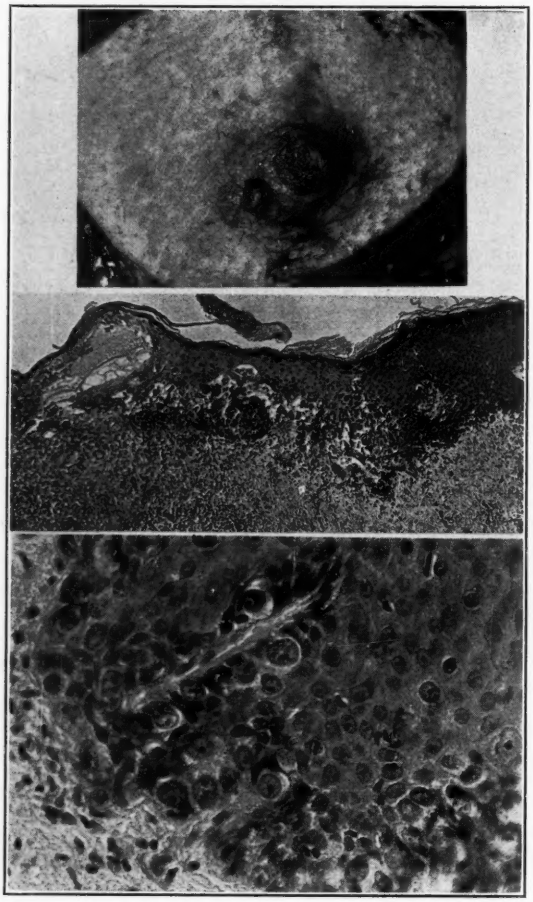

Fig. 15.—Photographs and photomicrographs of involvement of the nipple by Paget's cancer.

of the disease. This is also suggested by those patients who have noted a mass in the breast for months or years before noting changes in the nipple.

The symptoms in Paget's disease relate to the nipple whether or not a mass is found in the underlying breast. Itching, burning, pain, or soreness is noticed first but in some instances discharge, crust, or scabs were first observed. Fissure or ulceration usually developed in the cases which microscopically proved to be malignant, although in exceptional instances the nipple was red and large and finely granular.

In some instances there was gradual retraction and disappearance of the nipple, the nipple being replaced by an ulcer. In a few instances the area of ulceration was in the areola and not in the nipple itself.

Nearly 50 per cent of the patients were 50 years of age or over, and the majority were past the menopause. In 10 cases the patients were 65 years or over. The usual duration of symptoms was between 1 and 3 years. In 12 cases the duration was 5 years or over. Distinct papillary or warty projections of the epidermis covered by roughened but intact mucous membrane apparently bear no relationship to cancer.

The distinction between benign and malignant lesions of the nipple cannot be made clinically in cases of keratosis and ulceration in which a mass palpating like cancer is not found in the underlying breast. During the corresponding period in which 62 cases of Paget's cancer were observed, 82 benign lesions of the nipple were recorded. In 40 of these cases of keratosis, a few of which were complicated by ulceration and red granular nipple, the benign nature of the lesion was established by healing and disappearance of the lesion upon applications of petrolatum following cleansing of the nipple with soap and water over a period of three to four weeks. In the other 42 cases healing did not occur when such cleansing and protective measures were instituted. These cases, with 5 exceptions, were treated by excision, and microscopic study failed to reveal evidence of malignancy. In the 5 exceptional cases observed prior to 1920, simple mastectomy or the radical operation was performed because the lesions were considered clinically malignant although pathologic study failed to reveal evidence of carcinoma.

A pathologic study of the breast removed in cases of Paget's cancer of the nipple shows, in addition to the keratotic or ulcerated lesion of the nipple, dilatation of the larger ducts in the nipple zone. Occasionally these ducts are filled with blood or inspissated secretion. In other cases the dilated ducts are distended with cancer cells. In 1 case a small encapsulated lesion measuring 5 mm. was found just beneath the nipple. This was microscopically composed of cancer cells. The occurrence of a definite infiltrating mass in the mammary tissue outside the nipple zone occurred in slightly over 60 per cent of the cases. With few exceptions these cases also showed metastasis to the axillary lymph nodes. In 1 case the nipple and axillary nodes were involved and no cancer could be demonstrated in the mammary tissue.

The cases classified as Paget's cancer in the present series in every instance contained large cells with deep staining or vesicular nuclei and a large amount of pale staining cytoplasm in the epidermis of the nipple. Mitotic figures are frequent. In 2 cases the Paget cells were found only in the epidermis of the nipple or areola and no malignant cells could be found in the adjoining ducts or underlying mammary tissue. In the remaining cases the larger ducts were involved and the

cells in the nipple were infiltrated beyond the basement membrane. The ducts were lined by many layers of large malignant epithelium with necrotic debris or secretion in the enclosed lumen. Where the ducts only were involved in addition to the nipple, the growth in the ducts showed a histologic picture under low power suggesting the type of cancer loosely referred to as comedo or duct cancer. When the breast tissue was invaded, the microscopic appearance is that of Grade IV scirrhous carcinoma, but under high power the cells are larger, more irregular in shape, contain numerous mitotic figures and tumor giant cells, and in general resemble epidermoid carcinoma although no keratinization is found.

In the present series 22 cases of Paget's cancer clinically and on pathologic examination showed no mass within the breast proper. Three of these cases were treated by simple excision of the nipple and underlying ducts and fat. Three had simple amputations of the breast and the remainder were treated by radical mastectomy. One of the cases treated by local excision died of cancer 3 years later and 1 treated by simple mastectomy died of recurrent cancer 1 year later. The 2 remaining cases treated by excision were well 7 and 10 years later. In 1 both nipples were involved. In the 2 remaining cases receiving simple amputation, 1 died of metastasis 5½ years later and the other of old age after 8 years. In those cases treated by radical mastectomy in this group where the cancer was confined to the nipple and adjoining ducts, none so far traced has failed to survive the five-year period. Six have not been traced and 14 are cured.

There were 40 cases of Paget's cancer in which in addition to the nipple lesion there was a mass in the underlying breast, usually palpated before operation. All of these cases were treated by radical mastectomy. Twenty-three died of the disease within less than 5 years, the majority within a period of 1 or 2 years. Fifteen have not been traced. Two cases survived the five-year period. One of these died after 6 years, the other is living and well 10 years later.

Irradiation has failed to eradicate the disease as shown by cases ultimately treated by mastectomy, and Cohn has reported instances where irradiation was followed by healing of the lesion of the nipple but continued growth and spread of the disease occurred in the breast beneath. Keratosis, fissures, ulcerations, and red granular changes in the nipple should be treated by excision of the nipple zone with a margin of skin and a core of underlying ducts and fatty tissue, in those cases where the lesion fails to heal within three or four weeks after cleansing and protective measures. The excised tissue should be subjected to microscopic study and, if cancer is found, radical mastectomy is indicated. In those cases where cancer is not found in the underlying breast tissue, cures will be effected by this treatment. Where

cancer tissue is demonstrated in the mammary gland, the chances of the patient surviving the five-year period are less than 10 per cent (8 per cent in this series).

Paget's Cancer of the Ducts.—In the present series there were 23 cases of carcinoma which involved the larger ducts of the breast and which, on the basis of histology, could be related to the group of Paget's cancer just described. The tumor cells lined the ducts in broad sheets or multiple small papillary-like masses. The cells are

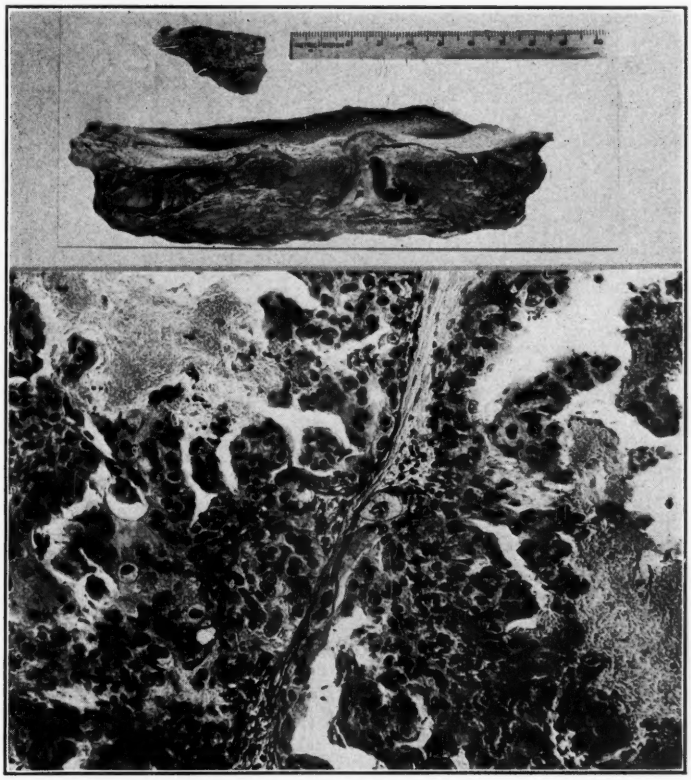

Fig. 16.—Gross specimen and photomicrograph of a case of duct cancer of the Paget type. The nipple was not involved in this case.

large and have an abundant cytoplasm with immense dense or vesicular nuclei with numerous mitoses. (Fig. 16.) Multinucleated giant tumor cells are common. The involvement of the larger ducts is similar to that found in Paget's disease in all respects except the nipple is not involved. This group of cases apparently represents the earliest stage of Paget's cancer which begins in the larger ducts within the breast proper rather than in the nipple. One-half of the cases gave a duration of symptoms of two months or less, a finding in keeping with this interpretation. None of the tumors exceeded 4 cm. in diameter. Fifteen of the 25 patients in this series, all of whom were treated by

radical operation, have been traced. Two were well after 4 years. Of the remaining 13, 7 died of metastases and 6 were well over 5 years.

Epidermoid or Pagetoid Cancer of the Breast.—In the present series there were 74 cases of cancer which resembled histologically the cases of Paget's disease of the nipple and Paget's cancer of the ducts. The age distribution in this group is similar to that for mammary cancer in general. The tumors were most often located in the midzone of the breast. With few exceptions they were embedded deep in mammary

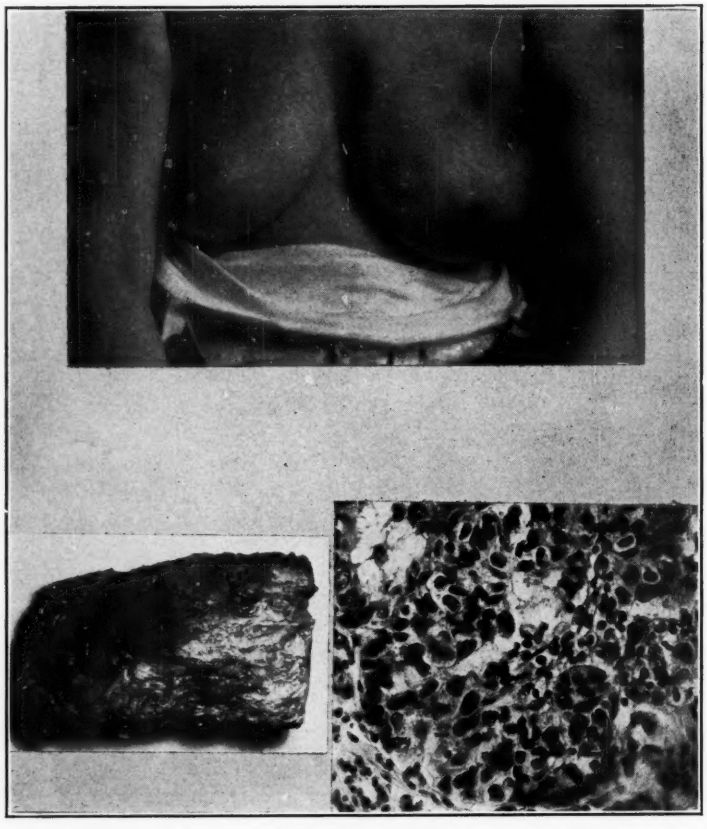

Fig. 17.—Photograph of the patient, gross specimen, and photomicrograph from a case of transitional cell (Pagetoid) carcinoma of the breast. The photomicrograph shows the resemblance of this form of cancer to epidermoid carcinoma.

tissue and one-fifth of the number were located in the lower hemisphere of the breast. The tumors resemble other forms of carcinoma in their tendency to grow rapidly without pain and ultimately to produce discoloration, edema, and ulceration of the overlying skin. The average size of the tumors in the series was 4.8 cm. The mass was usually regular on outline and circumscribed. (Fig. 17.) Most often it was freely movable. In nearly one-sixth of the cases the impression of benign cyst was obtained before operation and several were aspirated and a yellowish or bloody fluid obtained. In 5 cases the mass was

thought to contain multiple cysts, 1 giving the clinical impression of polycystic disease. In 5 cases the disease involved both breasts at intervals of 2 weeks, 1 year, 2 years (2 cases), and 6 years. The majority of the women affected had borne three or more children and an apparently significant number recalled a severe blow at the site where the tumor developed.

The most characteristic features are in the gross and microscopic pathology. In the gross pathology, with few exceptions, the tumor was classed as a cancer cyst. The tumor contained a distinct wall, sometimes uniformly thick and other times thinned at one or more portions. If the wall was relatively smooth and the cavity large, the cyst contained bloody fluid, a finding which rules out the possibility of a benign blue dome cyst. In other cases granular, grumous, necrotic, or pulpy material occupied the cavity. No distinct papillomatous mass was noted, a point which distinguishes them from papillary cancer.

Microscopic examination of the tumor tissue shows large highly malignant tumor cells, growing in sheets or coiled membranes. The nuclei are hyperchromatic, variable in size and shape, and contain frequent mitotic figures and binucleated forms. In 8 cases there was frank squamous cell cancer in the cyst lining. Some were apparently related to benign dermoid cysts and showed keratinization and pearl formation.

All of the 74 cases were treated by radical mastectomy, despite the fact that some were explored for a benign cyst. Twenty-two survived the five-year period and of these only 3 were known to have died ultimately of the disease. Thirty-eight died of the disease, with few exceptions in less than 4 years. The remaining cases were untraced. There are 32 per cent of five-year cures.

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Review of Recent Meetings

REVIEW OF THE THIRTEENTH ANNUAL MEETING OF THE PACIFIC COAST SURGICAL ASSOCIATION, LOS ANGELES, CALIF., FEB. 22-25, 1938

HENRY H. SEARLS, M.D., SAN FRANCISCO, CALIF.

Dr. Wayland A. Morrison, Los Angeles, Calif., in the President's Address, discussed the continued trend toward specialism in medicine, noting that the modern surgeon works hard and dies early. He advised less vocation and more avocation.

Dr. Howard C. Naffziger, San Francisco, Calif.: **Experiences With Injuries of the Intervertebral Disks and Ligamenta Flava.**—In Dr. Naffziger's absence this paper was presented by **Dr. Howard W. Fleming,** San Francisco, Calif. The essayist described the anatomy of the vertebral column and its fibrous and cartilaginous attachments with special reference to the ligamentum flavum and the intervertebral disks. The close relationship of the ligamentum flavum to the nerve roots was pointed out. Injury to this ligament results in hypertrophy and pressure on the neighboring nerve root. In other instances abnormal pressure on the vertebral column causes herniation of the soft nucleus pulposus through the thin posterior portion of the annulus fibrosus. The projection backward of this herniating fibrous material causes pressure on the cord or the branches of the cauda equina. The typical picture is that of a male in the active period of his life, who has a history of trauma, followed by sciatic pain which is aggravated by coughing or straining. The pain radiates to the outer side of the leg and to the dorsum of the foot. There is an absent or altered Achilles reflex on the affected side. Sensory changes may be noted on the outside of the calf; there is muscular weakness, and pain is present on straight leg raising. X-ray examination of the lower spine, following the administration of lipiodol intrathecally, shows a characteristic filling defect, which is diagnostic. Relief follows laminectomy and removal of the hypertrophied ligamentum flavum or herniated nucleus pulposus. In the discussion, **Dr. Harold Hitchcock,** Oakland, Calif., suggested spinal fusion following laminectomy in order to prevent weakening of the vertebral column by the operation. **Dr. Frederick Reichert,** San Francisco, Calif., felt that lipiodol left in the spinal canal might be injurious and suggested air as a substitute. In closing, Dr. Fleming agreed that the laminectomy might weaken the spine sufficiently to cause symptoms in a man who is doing heavy work, and felt that fusion might be necessary in such instances. He had not been impressed by the diagnostic accuracy of x-ray studies after the use of intrathecal air in place of lipiodol.

Dr. Fred R. Fairchild, Woodland, Calif.: **Supplementary Report on the Discussion of Appendicitis Given in 1930.**—Having reported a series of over 500 appendectomies in a first paper presented in 1930, Dr. Fairchild offered for comparison a new group of similar size which had accumulated since that time. He pointed out that, in both series, the mortality was eight times greater in the sec-

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ond half of life. There were no deaths in the second series when operation was performed within twenty-four hours of the onset of the attack. In his first series the mortality was 4.4 per cent; in the second, 1.37 per cent. He attributed the improvement to (1) less delay, (2) the use of a gridiron incision, (3) the reduction of the operative procedure to the simplest possible type in patients in the second half of life, and (4) the use of drainage rather than appendectomy in all patients for whom there was doubt in the surgeon's mind as to the safety of appendectomy. The paper was discussed by **Dr. William A. Taylor,** Ellensburg, Wash., who recommended a delay of from eight to fourteen days in all patients whose illness was of more than twenty-four hours' duration. He reported 3 deaths in 557 cases. **Dr. E. C. Moore,** Los Angeles, Calif., suggested the employment of regional or spinal anesthesia.

Dr. Alson R. Kilgore and **Dr. Leroy C. Abbott,** San Francisco, Calif.: **Sarcoma Following Benign Bone Lesions.**—The essayists pointed out the danger of secondary sarcomatous degeneration in some of the benign bone lesions and reported such a development in a case of chondroma. **Dr. E. I. Bartlett,** San Francisco, Calif., suggested the use of x-ray in central chondromas. **Dr. Donald V. Trueblood,** Seattle, Wash., discussed the pathologic phase of the problem and warned that a bizarre pattern in the benign lesion carries the threat of malignant degeneration.

Dr. John C. Wilson, Los Angeles, Calif.: **The Circulation of the Upper End of the Femur and Its Relationship to Trauma.**—Dr. Wilson pointed out that no blood vessels are found in the ligamentum teres in early or late life and, therefore, in fracture of the neck of the femur associated with rupture of the ligamentum teres, aseptic necrosis of the head is the common end-result. He felt that fracture of the neck of the femur in children is very serious and leads to grave disability. The immediate results are good, but in from ten to twenty months aseptic necrosis develops. Similar complications are found in late life.

Dr. E. C. Moore, Los Angeles, Calif.: **Chronic Cholecystitis with Reference to the Spastic Colon.**—Dr. Moore urged extreme care in the diagnosis of gall-bladder disease without stones. An irritable colon as the source of symptoms must be ruled out by therapeutic test. In the latter condition a definite history of colic or jaundice notably will be absent. X-ray examination, including barium enema and cholecystography, should always be employed. Gall-bladder disease and irritable colon cannot be differentiated by symptoms alone in many cases. The irritable colon, however, is functional and will respond to medical therapy. Dr. Moore emphasized here the importance, as in cases of peptic ulcer, of cooperation between the surgeon and the internist. If there is no history of acute gall-bladder colic or jaundice, he recommended medical treatment for colitis first as a therapeutic test. **Dr. Thomas Joyce,** Portland, Ore., suggested that the relief of gall-bladder disease might help a spastic colon. **Dr. L. R. Chandler,** San Francisco, Calif., noted improvement of gall-bladder function after a spastic colon had been returned to a normal state.

Dr. Edgar L. Gilcreest, San Francisco, Calif.: **Lesions of the Shoulder, with Special Reference to Unusual Ruptures of the Muscles of the Shoulder Girdle and Upper Arm.**—In most patients complaining of pain in the shoulder, extra-articular lesions, rather than arthritis, are the source of the trouble. Fraying or rupture of the supraspinatus tendon is not uncommon. Rupture of the biceps and triceps has been encountered frequently.

Dr. C. G. Toland and **Dr. William P. Kroger**, Los Angeles, Calif.: **Benign Tumors of the Stomach; Report of a Case.**—Myomas comprise the majority of benign gastric tumors. They rarely cause symptoms unless complications develop—such as ulceration, hemorrhage, pressure, or, rarely, malignant degeneration. If intraluminal, benign tumors may obstruct the pylorus; if extraluminal, they may cause symptoms by pressure. The authors reported a case of a large extraluminal myoma, arising by a pedicle from the posterior gastric wall and lying in the lesser sac. A filling defect seen by x-ray was first thought to be caused by carcinoma, but later the roentgenologist diagnosed a benign lesion. Peritoneoscopy identified the tumor as presenting below the greater curvature of the stomach. At operation the pedicle was transected and the tumor removed easily. It weighed 700 gm. The pathologic diagnosis was leiomyoma. The patient recovered. **Dr. Verne C. Hunt**, Los Angeles, Calif., described two origins of benign tumors—papillomas and adenomas from the epithelial layer, and myomas and fibromas from the connective tissue and muscular layers of the stomach wall. He noted that malignant degeneration is especially common in the case of papillomas.

Dr. William J. Norris, Los Angeles, Calif.: **Intestinal Obstruction in Infancy and Childhood.**—Dr. Norris reported 100 cases (treated by various surgeons in Los Angeles), including cases of intussusception, atresia, stenosis, obstruction from postoperative adhesions, malformed or imperfect anus, volvulus, obstruction from Meckel's diverticulum, intra-abdominal herniation, and stenosis from the ingestion of strong chemicals. Delay was considered the most important factor in mortality. No patient requiring resection recovered. He recommended, therefore, exteriorization for gangrenous loops. Factors which contribute to a reduction in mortality are: (1) early diagnosis, (2) avoidance of complicated procedures, (3) the preoperative treatment of dehydration and the use of measures to obtain decompression, and (4) the use of the least amount of surgery that can be done. **Dr. Otis Lamson**, Seattle, Wash., emphasized the seriousness of obstruction in infants and reported a case. **Dr. H. Glenn Bell**, San Francisco, Calif., stressed the importance of adequate preoperative care, the administration of parenteral fluids and blood transfusions, and reported several cases.

Dr. Paul C. Gunby, Seattle, Wash.: Congenital Pulmonary Cyst; Report of a Case.—The common error of calling this disease chronic empyema was emphasized and a case was reported of solitary congenital pulmonary cyst, which was finally recognized and cured by excision. **Dr. Frank S. Dolley**, Los Angeles, Calif., reported several similar cases and discussed the mechanics of their development.

Dr. Irving Wills and **Dr. P. A. Gray**, Santa Barbara, Calif.: **Diabetic Surgery. II. End-Results.**—These authors emphasized the fact that the diabetic patient, because of his metabolic defect, is more prone to infection, acidosis, and peripheral circulatory collapse than the normal person. Because of unfortunate experiences with the less radical procedure, they recommended high amputation, under spinal anesthesia, in cases of diabetic gangrene of the foot or leg. Postoperatively, the blood sugar determination should be made every four hours and sufficient insulin administered to maintain the blood sugar at from 100 to 150 mg. per cent. They recommended radical removal of thyroid tissue in toxic goiter and noted that such patients often require less insulin after operation. In emergencies, they operate at once unless the patient is in ketosis. Throughout the paper, they stressed the importance of cooperation with a good internist and laboratory technician. With such cooperation, any operation can be undertaken safely on the diabetic patient. **Dr. P. A. Gray**, Santa Barbara, Calif., emphasized the gravity of peripheral circulatory collapse and suggested the use of

a large amount of fluid to prevent or overcome it. **Dr. Verne C. Hunt,** Los Angeles, Calif., pointed out that anesthesia and operation temporarily upset the chemical balance and cause sudden wide variations in the blood chemistry.

Dr. Charles Fox, San Diego, Calif.: **The Treatment of Deep Infections of the Neck.**—Dr. Fox discussed the anatomy of the fascial spaces and pointed out that pus under the deep fascia cannot be demonstrated clinically. He felt that abscesses forming in this region do not give the impression of fluctuation because of the overlying fascia. He urged early incision and drainage and decried the delay in waiting for pointing. The deep fascia prevents the pus from coming to the surface. **Dr. E. I. Bartlett,** San Francisco, Calif., believed that infected teeth are most often the source of abscess formation under the deep fascia.

Dr. Philip K. Gilman, San Francisco, Calif.: **Malignant Disease of the Small Bowel.**—Cancer of the small bowel is twice as frequent in the male as in the female. It is rare, as compared to cancer in the colon. It is usually annular and constricting, and obstructive symptoms often are the first indication of the disease. Progressive pain after meals, colicky in character, occurring in the epigastrium above the umbilicus, associated with constipation and vomiting, suggests the development of chronic obstruction. A mobile mass may be felt; blood is usually present in the stool. The diagnosis usually can be made by x-ray examination. Glandular metastases may occur early. Treatment consists of resection, with removal of regional lymph nodes, but the prognosis is very grave. The essayist suggested a method of excision with extra-abdominal clamping of the transected ends and secondary intraperitoneal anastomosis after 24 hours. He reported three cases. **Dr. Thomas Joyce,** Portland, Ore., emphasized that pain is a prominent symptom in malignancy of the small bowel, and that occult blood is a frequent finding.

Dr. W. D. Kirkpatrick, Bellingham, Wash.: **Mesenteric Lymphadenitis in Relation to Intestinal Obstruction.**—Mesenteric lymphadenitis is most often found between the ages of 15 and 30 years; both tuberculous and nontuberculous types are noted, and either may be calcified. He reported a case of obstruction in an elderly patient, caused by a large, calcified mesenteric lymph node. **Dr. William J. Norris,** Los Angeles, Calif., noted that either caseation or calcification in mesenteric tuberculous adenitis tended to cause the formation of adhesions.

Dr. Samuel Robinson, Santa Barbara, Calif.: **A Case of Rupture of the Small Bowel without External Trauma or Pathology.**—The author reported a case of spontaneous rupture of the bowel, probably caused by extreme intra-abdominal pressure associated with athletic effort, forcing a portion of the bowel wall into a small inguinal hernial sac and rupturing it. He suggested that the mechanism was similar to that of an inner tube, bursting through a defect in an automobile tire. His patient had an extremely stormy postoperative course, developing several fecal fistulas, which were treated by means of intra- and extraluminal rubber disks sewed together, which temporarily closed the openings. The patient was finally sufficiently improved to permit reoperation and resection of the fistulous loops, and made an excellent recovery. **Dr. C. G. Toland,** of Los Angeles, Calif., having been in consultation on this patient, described the infinite care which the patient received in the effort to improve his condition to the point at which a secondary operation could be performed. **Dr. Edmund Butler,** San Francisco, Calif., reported a similar case in which intestinal contents were found in the sac of an inguinal hernia.

REPORT ON THE MEETINGS OF THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, BALTIMORE, MD., MARCH 30—APRIL 2, 1938

RAYMOND N. BIETER, M.D., ST. PAUL, MINN.

(From the Department of Pharmacology, the University of Minnesota Medical School)

THE pharmacology of sulfanilamide continues to be a question of major importance. An afternoon discussion meeting on this subject was conducted under the direction of **Dr. E. K. Marshall, Jr.**, and **Dr. Perrin H. Long**, Baltimore, Md. A considerable number of pharmacologists and other interested investigators participated. The first question considered was that of the therapeutic effects obtained in experimental infections in animals. It was agreed that even this question presented many difficulties, such as variations in the virulence of the organisms and the resistance of the host and how and when to administer the drug. An example of this latter difficulty is described. One large dose of sulfanilamide each 24 hours administered to mice infected with meningococci was no more curative than a mediocre serum. If the same total amount of the drug was given in two or more divided doses each 24 hours, the curative effects became marked.

The second question considered was that of therapeutic effects in patients. The most striking results have been obtained in the treatment of meningococcus infections. The next most satisfactory results have occurred in infections due to the beta hemolytic streptococcus. Less remarkable results, to date, have been observed in infections due to either the typhoid or the Welch bacillus, and in urinary tract infections due to gram-negative bacilli and staphylococci. In the treatment of pneumococcus lobar pneumonia the drug appears to be of no value, although in meningitis due to this same organism occasional good results have been obtained. It was also brought out that the drug shows its most marked therapeutic effect in acute infections of a highly invasive type.

The toxicity of sulfanilamide was the third question discussed. As is commonly known, the acute toxicity is rather low. Four investigators reported the lethal dose for 50 per cent of a series of mice to be from 3.5 to 4 gm. per kilogram of body weight. The chief toxic reactions observed clinically have been: (a) minor cerebral reactions, such as listlessness, dizziness, nausea, etc.; (b) fever and skin rashes; (c) cyanosis; and (d) the most dangerous reactions, namely, acute hemolytic anemia and agranulocytosis. To date, it has been quite difficult to duplicate these reactions in animals. No one has reported any changes in the red or white blood cells in animals, and only occasionally has cyanosis been observed in experimental work. The closest approximation to human toxic reactions was reported by **Dr. S. M. Rosenthal**, and **Dr. H. Bauer**, Washington, D. C., from the National Institute of Health. Their derivative, disulfanilamide, produced polyneuritis when used clinically. Returning to experimental conditions, they have found that this drug, and also sulfanilamide itself, commonly produces symptoms of polyneuritis and neuromuscular paralysis when administered daily for a period of a week to ten days to rabbits and chickens. On the other hand, with a sulfoxylate derivative of sulfanilamide, no such symptoms were noted. Several other investigators have also noted symptoms of peripheral neuritis in experimental animals receiving repeated daily doses of sulfanilamide.

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The fourth and last question considered was the mechanism of action of sulfanilamide. Studies to date have been concerned largely with the action of the drug against the beta hemolytic streptococcus. Its chief mode of action on this organism is believed to be one of bacteriostasis. A bactericidal action also can be obtained in vitro, but no evidence of this action has so far been noted in vivo. Other factors mentioned were the question of the drug combining with bacterial toxins, phagocytosis, and the possibility of the drug combining with the proteins of the body of the bacteria. It was also the opinion of a number of investigators that the natural resistance of the patient was a factor of considerable importance. In the final analysis, no definite conclusions could be drawn, because even in many patients treated, and to all intents and purposes cured, the beta hemolytic streptococcus persists for at least a number of days thereafter.

A number of interesting papers relating to general anesthesia were reported. **Dr. M. H. Seevers, Dr. W. H. Cassels,** and **Dr. T. J. Becker,** Madison, Wis., from the University of Wisconsin have been studying the problem of "ether convulsions" in rats and dogs. They considered the following factors: the anesthetic itself, pyrexia, and CO_2 retention. The anesthetic alone produced muscle twitchings in a single instance. Pyrexia alone produced no symptoms. Concentrations of CO_2 alone, especially above 20 per cent, elicited muscle twitchings more commonly. When these three factors were combined, muscular twitchings and convulsions occurred in more than 60 per cent of the animals. The convulsions, moreover, were frequently followed by death of the animals. Similar results were obtained in rabbits and dogs with the usual anesthetic concentrations of cyclopropane. Where the fundamental causes of these convulsions are unknown, they suspect that one of the chief factors is a lowering of blood pH, which is exaggerated by or associated with fever and rebreathing of CO_2, for a sufficient intake of oxygen will not prevent the convulsions.

Dr. B. H. Robbins, Dr. J. H. Baxter, Jr., and **Dr. O. G. Fitzhugh,** Nashville, Tenn., from Vanderbilt University, reported upon a study of the blood concentration of cyclopropane, in dogs, necessary to produce general anesthesia after premedication with morphine, sodium barbital and sodium amytal. The following table obtained from one of their slides illustrates the results they have obtained:

DRUG USED FOR PREMEDICATION AND DOSE IN MG. PER KG.	CYCLOPROPANE IN MG. PER 100 C.C. BLOOD NECESSARY TO PRODUCE			
	A ABOLITION OF ABDOMINAL REFLEXES (MG.)	B ABOLITION OF LID REFLEX (MG.)	C OCCURRENCE OF INTERCOSTAL PARALYSIS (MG.)	D OCCURRENCE OF RESPIRATORY ARREST (MG.)
None	16.8	20.6	25.5	28.0
Morphine, 2 mg.	8.7	15.1	25.0	29.9
Morphine, 5 mg.	6.0	12.4	21.1	28.5
Sodium barbital, 150 mg.	5.6	10.4	18.7	24.1
Sodium amytal, 45 mg.	5.0	6.9	17.0	25.2

It can be seen that the three drugs used for premedication all greatly lower the blood concentration of cyclopropane necessary to produce general anesthesia (second, third, and fourth planes of Stage 3), without greatly lowering the amount necessary for respiratory arrest. This evidence of increased safety is of great practical importance.

Dr. R. M. Waters, Dr. J. H. Bennett, and **Dr. M. D. Leigh,** Madison, Wis., from the University of Wisconsin, have studied the effect of combining atropine or scopolamine with morphine as a premedication for general anesthesia. Both alkaloids counteract, slightly, the mild depression of therapeutic doses of morphine on respiration. In addition, scopolamine seems to produce a more effective control of the morphine nausea. They believe that the optimum mixture is morphine 25 parts plus scopolamine 1 part (morphine sulfate 1/4 gr., and scopolamine hydrobromide 1/100 gr.) and that their maximum action is produced about one and one-half hours after hypodermic administration. This means, therefore, that for premedication, the drugs should be given from one to one and one-half hours before the general anesthetic.

Book Reviews

Textbook of Experimental Surgery. By J. Markowitz. Pp. 527, with 330 illustrations. Baltimore, 1937, Wm. Wood and Company. $7.

With the exception of a few facetious remarks which are of doubtful value in any scientific textbook, this work has been well done. The author has emphasized the physiologic aspects of surgery. He has also noted many advances in surgery which have developed through animal experimentation. Various procedures which have developed in the laboratory of surgical experimentation have been well described, some of which are now almost classical. The technique of operations upon animals has been thoroughly discussed and its relationship to human surgery considered. The entire book fills a very valuable place in surgery and should be in every laboratory of experimental surgery. It should be particularly valuable as a text for beginners in experimental work when any type of animal surgery is contemplated. It is an excellent book of its kind and favorably recommended.

Post-Graduate Surgery, Volume III. Edited by Rodney Maingot. Cloth. Pp. 5,584, with 1,015 illustrations. New York, 1937, D. Appleton-Century Company (printed in Great Britain). Three volumes sold only as set at $45.

The final huge tome (Volume III) of *Post-Graduate Surgery,* edited by Rodney Maingot, contains material upon a variety of topics. In sequence, the following constitute the subject matter of this book: medical aspects of surgery, hernia, plastic, obstetric, and cardiovascular surgery; lymphatic system, orthopedics, eye, ear, nose, endoscopic methods in surgery, malignant tumors of the pharynx and larynx, tonsils and adenoids, and retropharyngeal abscess, tongue, mouth and lips, esophagus and diaphragm, mandible, teeth, venereal disease, physical medicine, deep x-ray therapy, some aspects of general surgery, and finally some neurological and psychiatric aspects of surgery.

The sections on hernia by Ogilvie, on plastic surgery by Kilner, and on cardiovascular surgery by Cokkinis in which the operative procedure of Beck for coronary sclerosis is reviewed, the chapter by Sampson-Handle on the dissemination of malignant disease, and the sections on malignant tumors of the pharynx and larynx by Colledge, on tongue, mouth and lips by Cade, and that of O'Shaughnessy on the esophagus and diaphragm are easily among the better portions of the book and contain the newest and most authoritative expressions available upon these subjects. A brief but interesting and useful chapter is that of Manson-Bahr concerning elephantiasis. Medical opinion has apparently reversed itself upon the role of filaria in the occurrence of elephantiasis. A decade ago it was stated frequently that elephantiasis occurred only in the course of filariasis when streptococcal infection supervened. The experiments of Drinker and Field which indicate the susceptibility of lymphedematous tissues to infection lend increased credence to the original belief that the filaria obstructed the lymph vessels.

The chapters on the lymph vessels and their diseases by the editor, Maingot, appear to contain some unnecessary duplications of effort. Maingot emphasizes the

importance of surgery in the treatment of tuberculous lymph nodes, a practice which fell almost into disuse while roentgen treatment had its inning. The inclusion of chapters totaling almost three hundred pages on the eye, ear, and nose would indicate that the volume was probably intended for the general practitioner who does some surgery. For in this country, at any rate, the general surgeon rarely, if ever, meanders into these provinces of the surgical specialists. Many sections of the book have ample lists of excellent references which enhance the value of the work to those who seek more information upon the subjects under discussion. A detailed index facilitates access to the somewhat unrelated subject matter of the volume.

Books serve a variety of purposes. The greatest worth of this volume would seem to be as a ready reference manual to a great variety of subjects. The general surgeon will meet in it some authors who have made their reputations and others who have theirs still to make. However useful the volume may be in our day, it would take a venturesome prophet to predict that it will be read as long as Dennis', V. Bergman's, or Keen's systems of surgery, which serve many yet as important sources of helpful reference.

Praktikum der Chirurgie. By Professor O. Nordmann. Ed. 4. Paper. Pp. 811, with 409 illustrations. Berlin, 1938, Urban & Schwarzenberg. 25 R.M.

The purpose of the author in writing this text on the practice of surgery is to reach essentially the general practitioner who must know what surgery can offer a patient, even though he does not undertake performance of operation. The whole range of surgery is discussed in this volume exclusive of the eye and ear and gynecologic surgery. The clinical picture of disease entities is described with care and in detail. The indications for operation are discussed as well as choice of procedure. The technique of the more commonly performed operations is described briefly in a special section.

The author expresses, in the main, a rather conservative attitude concerning the management of most surgical disorders. The strength of the text lies in the extensive clinical and operative experience of the author; its chief weakness in that it is written by a single author, whose interest and experience of necessity cannot extend equally into all the manifold ramifications of surgery. The insertion of pertinent bibliographic references would have enhanced the value of the text. The arrangement of the subject matter could have been greatly improved upon by inserting descriptions of the operative procedure under their proper captions instead of adding them as an appendix to the text.

The author of this manual of surgery is obviously a thoughtful, critical, and practical man of large experience in the broad field of general surgery whose opinions concerning the management of surgical disorders merit justly the attention of the audience to which the book is especially directed.

Innere Sekretion und Chirurgie. By Hans Hanke. Pp. 326, with 18 illustrations. Berlin, 1937, Julius Springer, 23M.

This book by Hanke is an attempt to present the surgical aspects of the glands of internal secretion. There is presented in considerable detail a survey of present knowledge with respect to the physiology of these glands, a discussion of the symptomatology and pathogenesis of syndromes attributable to deficient and excess function, and a discussion of the possibilities of surgical intervention. In general the discussion is reasonably complete and the analysis critical and in line with conservative opinion.

The first third of the book deals with the physiology and pathology of the thyroid gland, and there follows in order a similar discussion of the parathyroids, thymus, islets of Langerhans of the pancreas, the adrenals, hypophysis, and the sex glands.

The undertaking is ambitious, and it is probable that no one man is competent to present an up-to-date analysis of the vast amount of work that is being done in the field of endocrinology. There are numerous references to the literature, and the German contributions to this field are fairly well summarized. American contributions have received relatively slight attention. This is unfortunate since most of the significant contributions in the field of endocrinology in recent years have come from American laboratories.

The printing is excellent, but the paper binding detracts somewhat from the appearance and usefulness of the volume.

Chemistry of the Brain. By Irvine H. Page. Pp. 444. Springfield, Ill., 1937, Charles C. Thomas, Publisher.

At a time when interest in problems pertaining to diseases of the nervous system is being revived on a broad scale, this book is a particularly welcome addition to the much too meager literature on the subject. In his comprehensive review the author, himself an active investigator in the field, has brought together pertinent data from widely scattered sources. Contrary to what might be expected from the title, the book is not a mere compilation of facts concerning the chemical composition of the brain, but treats the subject also from the broad biochemical and physiologic viewpoints. The material has been so well selected and appraised that it will serve as a useful reference for any worker requiring orientation in the field of brain metabolism, both in health and in disease.

The first chapter of the book is appropriately devoted to the life and works of Thudichum (1828-1901), "father of brain chemistry," and the older literature on analysis of the brain. Chapters then follow on each of the major chemical constituents of nervous tissue. Because of their unique prominence in such tissue, the lipids are given first place, in spite of the fact that little is definitely known regarding their specific physiologic rôles. Separate chapters are devoted to the sterols, the phosphatides, and the fatty acids. The cerebrosides are treated briefly in a special chapter. A much more extensive discussion of the carbohydrates of the brain and their intermediary metabolism is then presented. This is an especially valuable chapter because it touches upon many of the most vital problems of cerebral metabolism in health and disease. Discussion of the nitrogenous metabolism of the brain is confined to a consideration of those phases of the general subject of protein metabolism which are specially applicable to nervous tissue. While such nitrogenous metabolites as creatine, creatinine, choline, phosphagen, glutathione, and certain of the amino acids are undoubtedly of great importance in brain activity, it is pointed out that our knowledge of their exact significance is very meager. The physiologic and clinical significance of the electrolyte and gaseous metabolism of the brain is reviewed very thoroughly. The water metabolism of the brain is considered in a special chapter on physical and colloidal chemistry. Such topics as those pertaining to brain edema, water intoxication, epilepsy, and narcosis are included. In a chapter on the enzymes of the brain the author summarizes literature concerning variations in their content and activity in health and in certain diseases of the central nervous system.

Valuable miscellaneous data are assembled under the heading of comparative and developmental neurochemistry. Variations in the composition of brain tissue with age appear to have important clinical implications. The chapter on pathologic

gaseous metabolism and that on degeneration of the nervous system, as related to disturbances in nutrition, are of particular interest from the clinical point of view. Supplementing his own abbreviated discussions of brain metabolism in connection with the various topics already referred to, the author appends a special chapter by Quastel on oxidations in the brain. Data contained therein are very fundamental and are of great significance to brain physiology and pathology. The final chapter of the book is given over to a brief, philosophical discussion of "the brain and thought." Psychologists and philosophers may wish that this aspect of the subject could have been expanded, but the author wisely avoided treading where the "ice is too thin."

The Cerebrospinal Fluid. By H. Houston Merritt and Frank Fremont Smith. Pp. 333, with 17 illustrations. Philadelphia, 1937, W. B. Saunders Company, $5.

This is a book of over three hundred pages, based upon the study of some 20,000 cerebrospinal fluid specimens examined at the cerebrospinal fluid laboratory of the Neurological Unit of the Boston City Hospital and at the laboratory of Dr. James B. Ayer at the Massachusetts General Hospital. In addition, it contains a liberal number of references to the findings of other writers. The authors have taken pains to analyze the fluid findings only in those of their cases in which the diagnosis was well substantiated.

Short chapters are devoted to anatomy and physiology, technique, roentgenography, and methods of examination. Detailed consideration is given to chemistry and pathologic physiology and to the cerebrospinal syndromes in infections and diseases of the nervous system. The bibliography is extensive and a useful table is appended for the comparison of characteristic fluid findings in various conditions.

This is a well-written compilation, useful to the clinician and laboratory worker as a ready reference, rather than a presentation of new or particularly original material.

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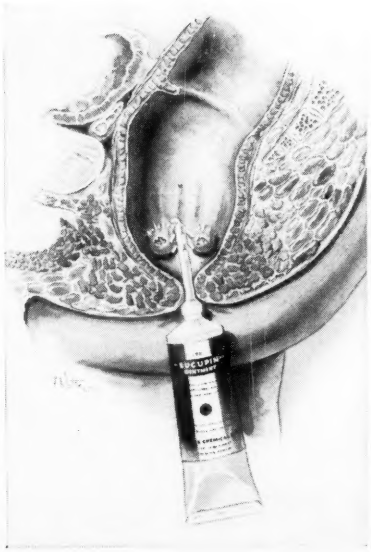

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